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Treatment of Anisometropic Amblyopia in Children with Automatic Frequency Conversion Laser

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Abstract

Objective: To evaluate the effectiveness of automatic frequency conversion laser (AFCLA) treatment in children with anisometropic amblyopia.

Methods: Prospective, noncomparative, interventional, noninvasive study was carried out in 102 anisometropic amblyopic children (4 to 13 years old) with the visual acuity ranging from 0.02 to 0.4 decimal in naked eyes. The area of the macula was irradiated by AFCLA through the conjunctiva from 200 cm distance for 240 sec with He-Ne laser light (wavelength 632.8 nm; automatic frequency conversion 10-35 Hz; average radiant power 0.98-3.5 mW; beam spot size at target 0.8 cm^2). AFCLA treatment was performed for initial 10-40 days, following up with 10-40 days consolidation therapy at 3,6,12 and 24 months, respectively. No occlusion was applied, and no additional medication was administered. Best-corrected visual acuity and refractive error in both amblyopic eyes (AE) and dominated eyes (DE) were measured.

Results: The amblyopes' visual acuity improved by 3 or more lines in 66.7% after the treatment of initial 10 to 40 days; in 94.2%, 99%, 100%, 100% after 10-40 days consolidation therapy at 3,6,12 and 24 months, respectively. The percentage of anisometropia (calculated difference in spherical equivalent <0.5 diopter (D) difference) decreased in 14.7%, 32.4%, 51.0% and 67.6% after 10-40 days consolidation therapy at 3, 6, 12 and 24 months, respectively. Treatment outcome was not related to age (P=0.86), prior treatment history of atropine (P=0.19) and visual training (P=0.62) but was related to better baseline visual acuity (P=0.01), less amounts of anisometropia (P=0.02) and prior treatment history of patching (P=0.03).

Conclusion: AFCLA improves visual acuity of children with anisometropic amblyopia. Following up 24 months, even anisometropic amblyopes with severe low vision are recoverable.

Keywords: Anisometripic amblyopia; Visual acuity; Automatic frequency conversion laser

Abbreviations AFCLA: Automatic Frequency Conversion Laser Treatment; VA: Visual Acuity; AE: Amblyopic Eye; DE: Dominant Eye

Introduction

Amblyopia is a developmental disorder of the central vision pathway [1-3], however, a broader understanding of pathophysiology of amblyopia remains questions [4]. It is the most common cause of visual loss [5] associated with a wide range of both monocular and binocular visual deficits [6] in children; it affects approximately 3-5% of the population [5]. Despite the success of refractive therapy [7,8], penalization [8-10], occlusion therapies [11-14], perceptual learning[15], and pharmacological treatment in improving monocular acuity of the amblyopic eye (AE), the majority of cases will need additional treatment to maintain the treatment outcome because there is a strong chance that amblyopia will recur [16]. The fact there is no guarantee that amblyopia will be cured emphasizes the importance of monitoring amblyopic patients closely once they have been successfully treated [16].

New technology and developed method of AFCLA give the possibility of cure to patients with anisometropia amblyopia [17-19]. AFCLA utilizes the low power laser with wave length at 632.8 nm; automatic frequency conversion10-30 Hz; average power 0.15 mW; spot area 4 mm^2. AFCLA mainly comprises a helium neon laser generator, a circular lightproof system installed on the output light path, a control circuit, a timer, and an angular rotation expander.

This prospective, noncomparative, interventional, noninvasive study tests the hypothesis of whether AFCLA therapy is effective in the anisometropic amblyopia with severe low vision or not.

Materials and Methods

Study design and patients

This prospective, noncomparative, interventional, noninvasive study, supported by Asia Pediatric Ophthalmologist Association, was conducted by the Radiant Children's Hospital Group. The protocol and HIPAA compliant informed consent forms were approved by the ethics committee of Radiant Children's Hospital Group (Beijing, China). The

parent or the guardian of each study patient was given a written informed consent.

Between January 2015 and December 2017, 102 participants (F=56, 54.9%) at the age 4 to 14 years old (the mean age 8.9 ± 2.4) with a history of treated anisometropic amblyopia (patching 100%, atropine 85.3% and visual training 13.8%) ranging from 0.04 to 0.5 decimal of best-corrected distance visual acuity were enrolled into this study at Beijing Radiant Children's Hospital. The mean visual acuity in the AE at study entry was 0.3 ± 0.1 decimal and was 1.0 ± 0.3 decimal in the DE. The baseline characteristics of cohort are provided in (Table 1).

Gender	**n (%)**
Female	56 (54.9)
Age	
4 to <5 years	3 (2.9)
5 to <6 years	7 (6.9)
6 to <7 years	7 (6.9)
7 to <8 years	10 (9.8)
8 to <9 years	23 (22.5)
9 to <10 years	11 (10.8)
10 to <11 years	17 (16.7)
11 to <12 years	5 (4.9)
12 to <13 years	10 (9.8)
13 to <14 years	9 (8.8)
Mean (SD) year*	8.9 (2.4)
Prior treatment for amblyopia	
Patching	102 (100)
2 years	54 (52.9)
3 years	29 (28.4)
4 years	9 (8.8)
5 years	10 (9.8)
Mean (SD) year*	2.8 (1.0)
Atropine	102 (85.3)
none	15 (14.7)
1 year	87 (85.3)
Mean (SD) year*	0.9 (0.4)
Visual Training	102 (13.8)
0 year	88 (86.3)
1 year	12 (11.8)
2 years	2 (2.0)
Mean (SD) year*	0.2 (0.4)
Best-corrected distance visual acuity (Decimal) in AE	
0.04	1 (1.0)
0.05	1 (1.0)
0.08	1 (1.0)
0.1	15 (14.7)
0.2	17 (16.7)
0.3	30 (29.4)
0.4	25 (24.5)
0.5	12 (11.8)
Mean (SD) visual acuity decimal	0.3 (0.1)
Best-corrected distance visual acuity (Decimal) in DE	
0.4	2 (2.0)
0.5	5 (4.9)
0.6	7 (6.9)
0.7	9 (8.8)
0.8	4 (3.9)
0.9	19 (18.6)
1	19 (18.6)
1.2	29 (28.4)
1.5	8 (7.8)
Mean (SD) visual acuity decimal	1.0 (0.3)
Interocular acuity difference mean (SD) lines	6.4 (2.5)
Anisometripia definition met	
Cylinder only (≥ 1.50D difference)	2 (2.0)
Spherical equivalent only (≥ 0.50D difference)	71 (69.6)
Spherical equivalent and cylinder	29 (28.4)

Table 1: Baseline Demographic and Clinical Characteristics at Enrollment (N=102).

Amblyopia was defined as best corrected VA 0.04 to 0.50 decimal and limited to cases associated with anisometropia only. The anosometropic amblyopia was characterized by an interocular acuity difference of 3 lines, anisometropia of ≥ 0.50 diopter (D) of spherical equivalent and/or ≥ 1.50 D difference of cylinder, and no myopia in the amblyopic eye. Patients were excluded if they had any measurable heterotropia in primary gaze at distance or near fixation in the prescribed spectacles or a documented history of strabismus; other concomitant eye or other systemic diseases that could impair vision. All participants had the parent or guardian maintain a calendar on which the treatment received each day was logged. The calendars were reviewed at follow up visits.

Ophthalmological examinations

Before they took part in the experiment, the participants were carefully diagnosed for potential ocular pathological defects and

strabismus; and determined their refraction through mydriasis optometry. A full orthoptic and ophthalmic examination were performed including intraocular pressure measurement, fundus examination, stereopsis, visual contrast, and cycloplegic refraction**20**. The visual acuity (VA) was assessed by crowded Chinese Tumbling E Chart. Imp. Improvement. The corneal light reflex test, cover-uncover test and alternated cover test were performed to assess the participants' ocular alignment. Detailed characteristics of these participants at the first day visiting were listed in (Table 1). The VAs and refractive error in both AEs and DEs were recorded in the interval of every 10-day in hospitals and following up at 3,6,12 and 24 months, respectively.

Laser treatment

Hospital treatments were performed for the initial 10-40 days using AFCLA (model: BP-E06, Beijing Tuoda Laser Equipment Co. Ltd. China, produced in Oct. 2007). BP-E06 laser treatment instrument product (AFCLA) belongs to classification number 160303 (visual treatment equipment) and management category is class II in rules for the Classification of Medical Device in China. It was registered as a medical device in China with the certificate number of Beijing Food and Drug Administration (standard) 2014 No. 2240691 and CE certificate number of 12 0230 QS/NB0. AFCLA mainly consists of a He-Ne laser remitter (tube length: 30 cm; diameter: 3 cm), a beam expander for transforming the direction of an optical path, a speed regulating motor for blocking an optical path, a timing control circuit for a motor rotation. The laser tube is mounted vertically on the tube holder inside AFCLA. A continuous wave (CW) with 632.8 nm wavelength and 0.1 cm diameter is emitted by the remitter at the average radiant power of 4.5-5.1 mW. The beam expander provides low-frequency switching of the linear beam (10-35 Hz; 1:1 duty cycle; beam spot size 0.6 cm^2; average radiant power 0.98-3.5 mW; irradiance ≤ 0.15 mW/cm^2); and the speed regulation motor automatically controls of 0.7-2.5mW average radiant power.

25 cm at the window of the beam expander, the beam is adjusted to the frequency conversion pulse train with 8 cm^2 diameter; 32 mrad divergence and 0.05 mW/cm^2 irradiance automatically. Beam spot size (0.4 cm^2) at target of macula is irradiated by AFCLA through the conjunctive from 200 cm distance in frontal of the eyeball for 240 sec with 38 mJ/cm^2 irradiant exposure at target. 10 treatments total per session delivered one every day over 10 days accumulates total dose of 380 mJ/cm^2 irradiant exposure. The optimum laser parameters, such as energy, duration, distance were determined by GB7247.1-2012/IEC60825-1: 2007, Safety of Laser Products Part I: Equipment Classification and Requirements of National Standard of the People's Republic of China. If there was a significant improvement after the initial 10-40th day treatment, participants were asked to return for 10-40 days consolidation therapy.

Data analysis

For each patient, the VA and refractive error improvement was computed. The resolution of amblyopia was defined as the VA in AE to be no more than one line worse than that in DE. The proportion of patients whose amblyopia resolved was computed and the 95% confidence interval calculated. The associations of age, prior treatment history (patching, atropine and visual training), VA, degree of anisometropia and type anisometropia (sphere only, cylinder only, both) with the improvement, resolution of amblyopia and treatment days were assessed using analysis of linear regression, respectively. All reported P values were two-tailed. SPSS version 22 was used for analyses.

Results

Visual acuity

The outcome examination was completed by 102 (100%) subjects. Visual acuity in AEs improved by an average of 3.2 ± 1.2 lines, 5.7 ± 1.8 lines, 7.2 ± 1.5 lines, 7.8 ± 1.6 lines and 8.0 ± 1.6 lines after the treatment at the 10-40 days, 3 months, 6 months, 12 months, and 24 months, respectively. Visual acuity data in AEs are listed in Table 2. Among the 102 patients having met the resolution criteria, the AE was one line worse than the DE in 3 (2.9%), 15 (14.7%), 47 (46.1%), 59 (57.8%), 59 (57.8%) and the same or better than the DE in 3 (2.9%), 1 (1.0%), 6 (5.9%), 22 (21.6%), 30 (29.4%) after the treatment at the initial 10-40 days, 3-months, 6-months, 12-months, and 24-months, respectively.

	40-day exam	3-month exam	6-month exam	12-month exam	24-month exam
Lines change from baseline, n (%)					
0 line better	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 line better	3 (2.9)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 lines better	30 (29.4)	5 (4.9)	1 (1.0)	0 (0.0)	0 (0.0)
3 lines better	28 (27.5)	7 (6.9)	1 (1.0)	2 (2.0)	2 (2.0)
≥ 4 lines better	40 (39.2)	89 (87.3)	100 (98.0)	100 (98.0)	100 (98.0)
Mean (SD) lines change	3.2 (1.2)	57 (1.8)	72 (1.5)	7.8 (1.6)	8.0 (1.6)
Distribution of visual acuity (Decimal), n (%)					
0.1	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	2 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

0.3	6 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.4	12 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.5	14 (13.7)	3 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
0.6	18 (17.6)	9 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)
0.7	28 (27.5)	8 (7.8)	1 (1.0)	0 (0.0)	0 (0.0)
0.8	10 (9.8)	17 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
0.9	9 (8.8)	23 (22.5)	19 (18.6)	1 (1.0)	0 (0.0)
1.0	2 (2.0)	28 (27.5)	31 (30.4)	21 (20.6)	14 (13.7)
12	0 (0.0)	13 (12.7)	48 (47.1)	61 (59.8)	60 (58.8)
2.	0 (0.0)	0 (0.0)	3 (2.9)	19 (18.6)	28 (27.5)
Mean (SD) visual acuity decimal	0.6 (0.2)	0.9 (0.2)	1.1 (0.1)	1.2 (02)	1.3 (02)
Interocular acuity difference lines, n (%)					
0 Me	3 (2.9)	1 (1.0)	6 (5.9)	22 (21.6)	30 (29.4)
1 Me	3 (2.9)	15 (14.7)	47 (46.1)	59 (57.8)	59 (57.8)
2 lines	7 (6.9)	28 (27.5)	29 (28.4)	20 (19.6)	13 (12.7)
3 lines	12 (11.8)	23 (22.5)	19 (18.6)	1 (1.0)	0 (0.0)
≥ 4 lines	77 (75.5)	35 (34.3)	1 (1.0)	0 (0.0)	0 (0.0)
Interocular acuity difference mean (SD) lnes	4.9 (2.1)	3.1 (1.7)	1.6 (0.9)	1.0 (0.7)	0.8 (0.6)
No. of treatment days, n (%)					
0	0 (0.0)	26 (25.5)	36 (35.3)	51 (50.0)	85 (83.3)
10	9 (8.8)	10 (9.8)	34 (33.3)	45 (44.1)	17 (16.7)
20	9 (8.8)	7 (6.9)	7 (6.9)	4 (3.9)	0 (0.0)
30	20 (19.6)	14 (13.7)	5 (4.9)	1 (1.0)	0 (0.0)
40	64 (62.7)	45 (44.1)	20 (19.6)	1 (1.0)	0 (0.0)
Mean (SD) treatment days	34 (9.7)	24 (17.0)	14 (15.0)	6 (7.1)	2 (3.7)

Table 2: Visual Acuity of Amblyopia Eye and No. 3 of Treatment Days (N=102).

VA in DEs improved by an average of 2 ± 1.4 lines, 2 ± 1.8 lines, 3 ± 1.9 lines, 3 ± 2.0 lines and 3 ± 2.0 lines after the treatment at the initial 10-40 days, 3 month, 6 month, 12 month, and 24 month, respectively. VA data in DEs are listed in (Table 3).

	40-day exam	**3-month exam**	**6-month exam**	**12-month exam**	**24-month exam**
Lines change from baseline, n (%)					
0	13 (12.7)	9 (8.8)	7 (6.9)	7 (6.9)	7 (6.9)
1 line better	36 (35.3)	31 (30.4)	31 (30.4)	31 (30.4)	31 (30.4)
2 lines better	27 (26.5)	20 (19.6)	20 (19.6)	20 (19.6)	20 (19.6)
3 lines better	14 (13.7)	19 (18.6)	19 (18.6)	18 (17.6)	18 (17.6)
≥ 4 lines better	12 (11.8)	23 (22.5)	25 (24.5)	26 (25.5)	26 (25.5)
Mean (SD) lines change	2 (1.4)	2 (1.8)	3 (1.9)	3 (2.0)	3 (2.0)
Distribution of visual acuity (Decimal), n (%)					
0.5	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.6	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.7	3 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.8	6 (5.9)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.9	4 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1	8 (7.8)	2 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)
1.2	22 (21.6)	11 (10.8)	4 (3.9)	4 (3.9)	3 (2.9)
1.5	57 (55.9)	88 (86.3)	97 (95.1)	98 (96.1)	99 (97.1)
Mean (SD) visual acuity decimal	1.3 (0.3)	1.5 (0.1)	1.5 (0.1)	1.5 (0.1)	1.5 (0.1)

Table 3: Visual Acuity of Dominated Eye (N=102).

Refractive error

Anisometropia was smaller than 0.50 D of spherical equivalent in 15 (14.7%), 33 (32.4%), 52 (51.0%), 69 (67.6%) after the treatment at the 3-month, 6-month, 12-month, and 24-month, respectively. Refractive error and anisometropia at enrollment and after treatments are provided in Table 4.

	At Enrollment	After 1st Treatment	After 3 months	After 6 months	After 12 months	After 24 months
Refractive error in AE, n (%)						
0.00 to <+1.00D	0 (0.0)	2 (2.0)	0 (0.0)	1 (1.0)	2 (2.0)	3 (2.9)
+1.00 to <+2.00D	0 (0.0)	2 (2.0)	14 (13.7)	35 (34.3)	51 (50.0)	57 (55.9)
+2.00 to <+3.00D	5 (4.9)	11 (10.8)	48 (47.1)	39 (38.2)	34 (33.3)	33 (32.4)
+3.00 to <+4.00D	20 (19.6)	27 (26.5)	24 (23.5)	19 (18.6)	10 (9.8)	6 (5.9)
+4.00 to <+5.00D	23 (22.5)	25 (24.5)	11 (10.8)	5 (4.9)	4 (3.9)	2 (2.0)
+5.00 to <+6.00D	19 (18.6)	22 (21.6)	3 (2.9)	3 (2.9)	1 (1.0)	1 (1.0)
+6.00 to <+7.00D	20 (19.6)	9 (8.8)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
+7.00 to <+8.00D	9 (8.8)	3 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
+8.00 to <+9.00D	6 (5.9)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD) spherical equivalent	5.2 (1.6)	4.3 (1.5)	2.7 (1.1)	2.2 (1.0)	2.0 (1.3)	1.7 (0.8)
Refractive error in DE, n (%)						
0.00 to <+1.130D	43 (42.2)	42 (41.2)	12 (11.8)	12 (11.8)	13 (12.7)	13 (12.7)
+1.00 to <+2.00D	42 (41.2)	43 (42.2)	62 (60.8)	64 (62.7)	64 (62.7)	65 (63.7)
+2.00 to <+3.00D	12 (11.8)	12 (11.8)	20 (19.6)	18 (17.6)	18 (17.6)	19 (18.6)
+3.00 to <+4.00D	3 (2.9)	3 (2.9)	3 (2.9)	4 (3.9)	5 (4.9)	3 (2.9)
+4.00 to <+5.00D	1 (1.0)	1 (1.0)	4 (3.9)	3 (2.9)	1 (1.0)	1 (1.0)
+5.00 to <+6.00D	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)
Mean (SD) spherical equivalent	1.2 (1.0)	1.2 (0.9)	1.6 (0.9)	1.5 (0.9)	1.5 (0.8)	1.4 (0.7)
Anisometropia (Calculated difference in spherical equivalent), n (%)						
0.00 to <+0.50D	0 (0.0)	0 (0.0)	15 (14.7)	33 (32.4)	52 (51.0)	69 (67.6)
+0.50 to <+1.00D	0 (0.0)	0 (0.0)	21 (20.6)	25 (24.5)	25 (24.5)	17 (16.7)
+1.00 to < +2.00D	0 (0.0)	11 (10.8)	40 (39.2)	34 (33.3)	17 (16.7)	8 (7.8)
+2.00 to <+3.00D	23 (22.5)	30 (29.4)	20 (19.6)	6 (5.9)	7 (6.9)	7 (6.9)
+3.00 to <+4.00D	30 (29.4)	32 (31.4)	4 (3.9)	4 (3.9)	1 (1.0)	1 (1.0)
+4.00 to <+5.00D	16 (15.7)	18 (17.6)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
+5.00 to <+6.00D	20 (19.6)	6 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
+6.00 to <+7.00D	8 (7.8)	3 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

+7.00 to <+8.00D	5 (4.9)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD) spherical equivalent	4.1 (1.5)	3.3 (1.3)	1.3 (0.9)	0.8 (0.8)	0.6 (0.7)	0.4 (0.7)

Table 4: Refractive Error and Anisometropia at Enrollment 8 and after Treatments (N=102).

Resolution of amblyopia

Resolution of amblyopia in naked AEs was related to prior history of patching (P=0.03), baseline VA of naked AEs (P=0.01), baseline interocular acuity difference (P=0.02), baseline refractive error (P=0.05) and the number of days at the initial 10-40-day treatment (P=0.01), but was not related to age (P=0.86), sex (P=0.35), prior history of visual training (P=0.62), prior history of atropine (P=0.19), and baseline best-corrected VA (P=0.33). Resolution of amblyopia in best-corrected AEs was related to prior history of atropine (P=0.05) and Patching (P=0.03), baseline best-corrected VA (P=0.01), baseline interocular acuity difference (P=0.03), baseline refractive error (P=0.03) and the number of days at the initial 10-40-day treatment (P=0.01), but was not related to age (P=0.07), sex (P=0.83), prior history of visual training (P=0.30), and baseline VA of naked AEs (P=0.08). The visual acuity in AE after the initial 10-40-day treatment to baseline factors was listed in (Table 5).

Baseline Factors	Naked AE				Best-corrected AE			
	ANOVA		Coefficient		ANOVA		Coefficient	
	F	Sig.	t	Sig.	F	Sig.	t	Sig.
Age (Years)	-	-	0.17	0.86	-	-	2.	0.07
Sex	-	-	-0.93	0.35	-	-	0.22	0.83
Prior History of Visual Training	-	-	0.50	0.62	-	-	1.05	0.30
Prior History of Atropine	-	-	-1.32	0.19	58.32	0.01	2.03	0.05
Prior History of Patching	21.67	0.01	-2.27	0.03	58.32	0.01	-2.24	0.03
Naked VA	21.67	0.01	6.36	0.01	-	-	1.79	0.08
Best-corrected VA	-	-	0.98	0.33	19.66	0.01	4.32	0.01
Interocular Acuity Difference	21.32	0.01	-2.40	0.02	19.66	0.01	2.18	0.03
Refractive Error	21.32	0.01	-2.00	0.05	19.66	0.01	-2.20	0.03
No. of Days at Initial 10-40 Day Treatment	21.67	0.01	2.62	0.01	19.66	0.01	3.33	0.01

Table 5: Visual Acuity in AE after Initial 10-40 Day Treatment to Baseline Factors (N=102).

Discussion

In this prospective, observational study of 102 children with anisometropic amblyopia aged from 4 to 14 years old, we found that AFCLA treatment improved AE visual acuity an average of 3.2 ± 1.2 lines; visual acuity improved from baseline by 3 or more lines in 66.7% of the patients after the initial 10-40 days treatment. Visual acuity in AEs improved by an average of 5.7 ± 1.8 lines, 7.2 ± 1.5 lines, 7.8 ± 1.6 lines and 8.0 ± 1.6 lines at 3 month, 6 month, 12 month, and 24 month, respectively. The AE was one line worse than the DE in 59 (57.8%), 59 (57.8%) and the same or better than the DE in 22 (21.6%), 30 (29.4%) at 12-month, and 24-month, respectively. These results demonstrate that AFCLA therapy is an effective amblyopia therapy modality to accelerate the improvement of children with anisometric amblyopia.

Reports on the application of hospitalization for the management of anisometropic amblyopia have been limited. In most of the studies, atropine [9,10], patching [14,20,21], atropine combined with spectacles [8,22], spectacles combined with patching [23] or special training *via* equipment [24-27] had been used. The daily hospital treatment using AFCLA accelerated the improvement of anisometropic amblyopia eyes. However, we did not preclude that this therapy might also affect sensory improvements, cellular function improvements in the amblyopic eyes or the molecular underpinnings of synaptic plasticity in the visual cortex [17-19,28,29]. How to maintain the visual acuity for a long time stabling to prevent recurrent was a key point [16,30,31]. Our results showed that, following up with 10-40 days consolidation therapy at 3,6,12 and 24 months, respectively, did help to maintain the visual acuity and further improve the visual acuity until the 24-month stabilization.

AFCLA device uses the optimized sensitive wavelengths 632.8 mm lasers, the optimized suitable optical density and energy of laser for ganglion, cone, and rod cells in the retina. These not only enhances the activity of ganglion, cone, or rod cells, but also improves the local micro-circulation and increases the local metabolism [17,28,29] by the

mechanisms: i. mitochondria as the subcellular targets of far-red to near-infrared [32,33]; ii. cytochrome C oxidase inside mitochondria serves as the primary photoacceptor [34,35]; iii. cytochrome C oxidase as the main photoacceptor mediator [34]. The design of AFCLA series is based on sensitive physiological needs in different parts of the visual pathway. The stimulation using 10-30 Hz of automatic cycle pulse wave can enhance the sensation and conduction of visual information, increase the sensing and processing capacity for information in visual cortex.

Resolution of amblyopia was related to prior history of patching 102 (100%) and atropine 102 (85.3) effects, but it was not related with prior history of visual training 102 (13.8%). The improvement in VA of the AE from baseline to best measured VA averaged 2.2 lines in the patching only [36] and 4.5 lines in the atropine plus correction [37]. In this study, the improvement in VA of the AE from baseline to best measure VA averaged 5.7 ± 1.8 lines, 7.2 ± 1.5 lines, 7.8 ± 1.6 lines and 8.0 ± 1.6 lines after the treatment at 3 month, 6 month, 12 month, and 24 month, respectively. Resolution of amblyopia was also related to the number of day's treatment at the first initial 10-40-day treatment (P=0.01). If treatment days were longer, the stabilization was easier, and results were better.

The time course for the improvement of the visual acuity to the best AE (line change from baseline to ≤ 4 lines better) was variable in this study. The majority (87.3%) of patients stopped improving after 3 months, 10.7% patients stopped improving after 6 months, but two patients only reached 3 lines better even after 24 months. The explanation for the visual acuity improvement of these two patients was related to their low VA of naked AE (P=0.01); best-corrected AE (P=0.01); baseline interocular acuity difference (P=0.03) and baseline refractive error effect (P=0.03) at the baseline.

Conclusion

AFCLA therapy at first initial 10-40 days made significant improvements for the VA of both AEs and DEs. Majority of both eyes stabilized in the 3-month. The best-corrected VA was constantly improved after the consolidation therapies. AFCLA therapy improved VA in anisometropic amblyopic children at the first initial 10-40 days hospitalization. Following up by 10-40 days consolidation therapies with 3-, 6-, 12- and 24-months interval, even the anisometropic amblyopia with low VAs was recoverable.

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