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Yuan Y. Zhu C. Wang P. Hu X. Yao W. Huang X. Ke B.

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Research Article

Alternative Flicker Glass: a New Anti-suppression Approach to the Treatment of Anisometropic Amblyopia

Ying Yuan\textsuperscript{a,b}, Chengcheng Zhu\textsuperscript{c,d}, Peng Wang\textsuperscript{a,e}, Xiaojun Hu\textsuperscript{b}, Wenbo Yao\textsuperscript{f}, Xinhui Huang\textsuperscript{f}, Bilian Ke\textsuperscript{a,b,}\textsuperscript{*}

\textsuperscript{a} Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai, China

\textsuperscript{b} National Clinical Research Center for Eye Diseases; Shanghai, China

\textsuperscript{c} Shanghai Key Laboratory of Fundus Disease, Shanghai, China

\textsuperscript{d} Shanghai engineering center for visual science and photomedicine, Shanghai, China;

\textsuperscript{e} Shanghai engineering center for precise diagnosis and treatment of eye diseases, Shanghai, China

\textsuperscript{f} Shanghai Eye Disease Prevention and Treatment Center, Shanghai 200040, China

Short Title: a New Anti-suppression Approach to the Treatment of Amblyopia

\textsuperscript{*}Corresponding author and address for reprint requests

Bilian Ke, MD
Department of Ophthalmology
Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine
100 Haining Road
Shanghai 200080, China
TEL: +86-21-63243071
E-mail: kebilian@126.com

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Abstract

Introduction: Amlyopia always presents with monocular and binocular dysfunction. In this study, we aim to investage the efficacy of alternative occlusion using liquid crystal glasses versus continuous occlusion therapy using traditional patches for treating amblyopia.

Methods: Eligible subjects with anisometric amblyopia were randomized into two groups: alternative flicker glass (AFG) or patching group. In the AFG group, subjects were instructed to wear the flicker glasses for 1 hour a day. The AFG is a lightweight spectacle frame with liquid crystal lenses that provide direct square-wave alternating occlusion, which were pre-programmed at temporal frequency of 7Hz. In the patching group, the patients were prescribed to wear traditional patches for 2 hours a day. The best corrected visual acuity (BCVA), contrast sensitivity function (CSF) and stereoacuity were measured at the baseline, 3 and 12 weeks.

Results: In this pilot study, a total of forty children were recruited, with twenty in the AFG group. Mean BCVA improved by 0.17±0.14logMAR (95% CI=0.10 to 0.23) in the AFG group, while 0.18±0.18logMAR (95% CI=0.09 to 0.26) in the patching group from baseline to 12 weeks. The improvement of BCVA in both groups were significant (both $P<0.01$), while no significant difference between the groups ($P=0.82$). The CSF of both low and high spatial frequencies exhibited significant improvement at 12 weeks in the AFG group ($P<0.01$, respectively), while just have a significant improvement at low spatial frequency in the patching group ($P<0.01$). The stereoacuity significantly improved by 504.00±848.00 (95% CI= -900.88 to -107.12) arc seconds in the AFG group ($P<0.05$), while 263.50±639.55 (95% CI= -562.82 to 35.82) arc seconds in the patching group ($P>0.05$).

Conclusion: Alternative flicker glass was effective in improving both monocular and binocular function, which was most likely achieved by reducing the suppression and promoting binocular fusion. This therapy exhibited promise as an alternative method for amblyopia treatment.
Introduction

Amblyopia is a neuro-developmental disorder of the visual cortex, which presents with monocular and binocular dysfunction. This disorder is usually associated with abnormal visual experience, such as anisometropia or strabismus, during early childhood. Traditional amblyopia treatment, including patching or penalization of the sound eye, aimed at the recovery of monocular function [1]. However other visual functions remain deficient in clinically treated amblyopia such as contrast sensitivity at high spatial frequencies and stereoacuity [2,3]. It also had a high risk of recurrence when the treatment was stopped, which may be associated with the residual abnormal binocular vision after monocular treatment [4,5]. Additionally, traditional patching treatment for amblyopia had a low compliance for the psychosocial side effects [6]. Therefore, a new treatment method that could not only improve visual acuity of the amblyopic eye but also provide repeated binocular visual experience is needed.

Our understanding of the visual deficits in amblyopia has changed in recent years [7]. It was believed that the visual input from the amblyopic eye was suppressed, resulting in monocular and binocular vision deficits in amblyopia. In support of this, several studies have found that both the monocular and binocular function of the amblyopia could improve when the input in the sound eye was artificially attenuated [8-10]. The adult amblyopic cortex had the potential to improve after perceptual learning, although it was outside of the critical period of visual development [11]. Additionally, the visual acuity in amblyopia of the animals could be restored when the inhibition of the visual cortex was reduced [12]. Together, all of these studies on humans and animals suggested that the vision deficit in amblyopia was caused by the suppression mechanisms in the visual cortex rather than a loss of cellular function. Furthermore, the relationship between the degree of amblyopia and strength of suppression was also investigated [2]. It was found that, the stronger the suppression, the greater the difference between the interocular acuity and poorer binocular function [7,13]. According to this view, anti-suppression and promoting binocular function should be the key point for treating amblyopia.

In this study, we used a novel treatment that targeted binocular interaction in amblyopia, which presumably decrease the suppression of amblyopia. The alternative flicker glass (AFG) is an electronic LCD display, which could alternatively present images to the sound and amblyopic eyes at a customized rate. The flicker frequency was pre-programmed at 7Hz, which has been shown to be beyond the time course for interocular suppression in amblyopia [14]. It allowed the subjects to experience binocular vision in such an alternative flicking rate. Therefore, the goal of this study was to evaluate whether the AFG, with 7Hz flicker therapy, could promote monocular and binocular function. In this report, we evaluated the best corrected visual acuity (BCVA), contrast sensitivity function (CSF), and stereoacuity before and after the treatment.

Materials and Methods

Subjects
Eligible children with anisometropic amblyopia, from 7 to 13 years old, met with the inclusion criteria and were enrolled in the study. The children were outpatients at Ophthalmology unit of Shanghai General Hospital. The study protocol complied with the requirements of the Institutional Review Board of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine and adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from the subjects and at least one of the subject’s legal guardians before participation. Forty subjects underwent a complete ophthalmic examination including cycloplegic retinoscopy, fundoscopy, and slit-lamp biomicroscopy before entering the study. The inclusion criteria were: BCVA of 0.70logMAR to 0.20logMAR in the amblyopic eye, with two lines or more of difference between the two eyes, and no amblyopia treatment three month prior to the study except refractive correction. The subjects had been wearing spectacle correction for 12 weeks prior to the study. Those with intraocular surgery, high myopia (larger than -6.00D) or hyperopia (larger than +9.00D), ocular disease as the cause of the reduced visual acuity, strabismus, or a family or personal history of seizures were excluded. Anisometropia was defined as an interocular spherical refractive error difference of 1.50 D or more or a cylindrical difference of 1.00 D or more.

Device

The AFG is a spectacle frame with lenses of liquid crystal glass, which were provided by EyeTronix, Inc. The liquid crystal lenses comprise a gel with organic molecules suspended in between two thin plates coated with thin polarized film. An electronic shutter controlled by a preprogrammed microchip allows for accurate and fast alternating rate of occlusion. In this study, the flicker rate is set at 7Hz with a 50% duty cycle between the right and left eyes. In the patching group, non-amblyopic eye was prescribed to wear occlusion patches combined with optimal refractive correction (if needed).

Treatment procedure and follow-up visits

Each subject was randomly assigned to AFG or patching group. In the AFG group, subjects were asked to wear the AFG for 1 hour a day, 7 days a week. Additional prescribed corrective glasses was wore when using AFG treatment. In the patching group, subjects were asked to wear the patches for 2 hours a day, 7 days a week. Follow-up visits were conducted at 3 and 12 weeks after treatment. Each subject underwent a comprehensive ophthalmological examination, including BCVA (logMAR chart), CSF (CSV-1000E charts, Vector Vision) and stereocuity (Titmus test) at baseline as well as the following scheduled visits. The Titmus test is consisted of 9 circles ranging from 800 arc seconds to 40 arc seconds. Test started with the gross stereocuity, and inability to correctly identify the fly was recorded as ‘nil’ stereocuity.

Statistical analysis

Subjects who completed each follow-up visit were included in the analysis. The variables were presented as the mean ± standard deviation. Participants with nil stereocuity (>3000 arc sec) were recorded as 3000 for the purpose of analysis. All statistical evaluations were performed using SAS version
9.2 (SAS Institute). A paired t-test was used to assess BCVA, CSF and stereoacuity before and after treatment for each group. An independent t-test was used to analyze BCVA, CSF and stereoacuity improvement between the AFG and patching groups. P < 0.05 was considered statistically significant. All tests were two-tailed.

**Results**

**Visual acuity**

Of the forty children recruited, twenty subjects were randomly assigned to the AFG group, while twenty subjects to the patching group. Baseline clinical parameters were similar in both groups (shown in Table 1). After AFG therapy, there was a significant improvement of BCVA (shown in Fig. 1). At the baseline, the mean BCVA was 0.45±0.20logMAR (95% CI=0.35 to 0.54), while at 3 and 12 weeks, it improved to 0.37±0.20logMAR (95% CI=0.27 to 0.46) and 0.28±0.19logMAR (95% CI=0.19 to 0.37) (both P < 0.01, compared to the baseline) in the AFG group. In the patching group, the mean BCVA improved to 0.43±0.20logMAR (95% CI=0.34 to 0.52) and 0.35±0.18logMAR (95% CI=0.27 to 0.43) at 3 and 12 weeks, which was significantly different from the baseline (0.53±0.25logMAR (95% CI=0.41 to 0.65), P < 0.01, P < 0.05, shown in Fig. 1). There was no significant difference of BCVA between AFG group and the patching group at baseline and the scheduled follow-up visits (P = 0.25, 0.30, 0.24, respectively).

**Contrast sensitivity function**

Furthermore, we tested the CSF of 3, 6, 12 and 18 cycles per degree spatial frequencies at baseline and the follow-up visits (shown in Fig. 2). When compared with the baseline, the CSF of all spatial frequencies showed a significant improvement, except for 18 cycles per degree spatial frequency at the visit of 3 weeks in the AFG group (P < 0.01, P < 0.01, P < 0.01, P=0.07). At the 12-week visit, the CSF of 18 cycles per degree spatial frequency had a significant improvement (P < 0.01, compared with the baseline). In the patching group, there was a significant improvement of CSF only in the spatial frequency of 3 cycles per degree at the visits of 3 and 12 weeks (both P < 0.01). The improvement of CSF of 6, 12 and 18 cycles per degree spatial frequencies is larger in the AFG group than that in the patching group (P < 0.01, P < 0.01, P < 0.05, shown in Fig. 3).

**Stereoacuity**

After treatment, the mean Titmus stereoacuity significantly improved to 210.00± 185.19 (95% CI=123.33 to 296.67) arc seconds and 105.00±75.57 (95% CI=69.63 to 140.37) arc seconds at the visits of 3 and 12 weeks in the AFG group when compared with the baseline (609.00±860.54 (95% CI=206.26 to 1011.74) arc seconds, P < 0.05, respectively; shown in Fig. 4). In the patching group, the stereoacuity was 576.00± 637.15 (95% CI=277.80 to 874.20) arc seconds at the baseline. At the follow-up visits of 3 and 12 weeks,
the stereoacuity had improved to 407.00±262.24 (95% CI=284.27 to 529.73) arc seconds ($P$=0.15, shown in Fig. 4) and 312.50±276.88 (95% CI=182.92 to 442.08) arc seconds ($P$=0.08, shown in Fig. 4). None of the subjects stated significant uncomfortable symptoms including headache, eyestrain or dizzy and nausea after wearing the AFG or the patch in this study.

**Discussion**

The initial result of the AFG therapy was very encouraging with the significant improvement of both monocular and binocular visual function. Additionally, the CSF of high spatial frequency had got an improvement after AFG treatment. This study suggested that 1-hour of 7Hz alternative occlusion is effective in treating anisometropic amblyopia, which was not inferior to 2-hours of occlusion.

In our study, we found the improvement of BCVA after AFG treatment with 7Hz. At the alternative flicker rate of 7Hz, subjects presented with fusion or superimposition of the images because the time course of interocular rivalry suppression in amblyopic subjects was longer than 150 ms [14]. Therefore, the 7Hz (143ms) alternation frequency of AFG fulfilled the requirement for an anti-suppression therapy with bilateral sight [15]. Eric once used a similar electronic rapid alternate occlusion with liquid crystal lenses flicking at 5Hz to treat intermittent central suppression, which was effective in reducing suppression within the cortex [16]. In this study, the improvement of BCVA in the AFG group was not inferior to the patching group although the occlusion time is much less. This proved that binocular treatment could also have an effect on monocular visual acuity. Additionally, the subjects were mainly older children, who were beyond the critical period of visual development in this study. This may suggest that the visual acuity of amblyopia in older children still had the potential to recover [17]. Previous studies had also applied liquid crystal glass to the treatment of amblyopia and found the improvement of visual acuity [18-20]. But it was different from this study. In most studies, liquid crystal glass has been applied monocularly with the same aim as patching therapy, to improve visual acuity of the amblyopic eye. Wang and his colleagues used flicker glasses, set at 30-second opaque/transparent intervals for 4 hours a day, to treat amblyopia [18]. Spierer demonstrated that it was effective of liquid crystal glass to the treatment of amblyopia by using the procedure of 40 seconds occlusion and 20 seconds open of each minute with 5 hours of occlusion in a day [19]. Therefore, it may not have an act on the binocular fusion. This study could give insight of the efficacy of 7Hz AFG in improving amblyopic eye visual acuity in older children.

We found that AFG therapy could improve the CSF of the amblyopic eye, including both the low and high spatial frequencies, which was different from the occlusion treatment. Before the treatment, the deficit of the CSF in anisometropic amblyopia crossed all ranges of spatial frequencies, which was consistent with previous studies [21, 22]. According to Nicholas, the CSF is a basic characteristic of the visual system and the most important recording in spatial vision [23]. A previous study demonstrated that the monocular contrast sensitivity might be associated with the binocularity of neurons in the early visual pathway [24]. Treatment for binocular functions may be necessary for the recovery of monocular spatial vision. It was reported that the CSF of the amblyopic eye improved after the perceptual learning or vernier task, which
could diminish the cortical suppression [25-27]. At the third week, there was a significant improvement in the CSF of 3, 6, 12 cycles per degree spatial frequencies in the AFG group, while only in the 3 cycles per degree spatial frequency CSF in the patching group. The improvement of 18 cycles per degree spatial frequency was insignificant in both groups. It was known that higher spatial frequencies of the CSF developed very quickly in infancy and matured by 3 to 6 years of age, while lower spatial frequencies matured around the ages of 9 to 12 years [28, 29]. Therefore, the recovery of high spatial frequency may require longer observation and more treatment. With the extension of the observation time, the CSF of 18 cycles per degree spatial frequency also presented a significant improvement in the AFG group, while still insignificant improvement in patching group. This indicated that binocular treatment may have advantage in recovering high spatial frequency contrast sensitivity. However, the high spatial frequency of the CSF in the amblyopic eyes still had some deficits compared with the fellow eyes after 12-week treatment. The signal of high spatial frequency was thought to be input from the parvocellular pathway, while the low spatial frequency was from the magnocellular pathway [21]. The residual deficits in the high spatial frequency may be associated with the mis-wiring of the cortical neurons in the visual processing or down-weighting of the high spatial frequency channels of the amblyopic eyes.

The stereoaucuity significantly improved after AFG treatment in this study. It agreed with previous report that binocular treatment could induce stereoaucuity recovery [30, 31]. Additionally, an interesting finding in our study was that the improvement in the stereoaucuity was not parallel to the improvement in the visual acuity in the AFG group. One subject did not have improvement in the visual acuity, although the stereoaucuity reached 140 seconds. Conversely, we found that there is no significant improvement of stereoaucuity, although the visual acuity significantly improved in the patching group. This indicated that AFG treatment led to recovery of the binocular function first, which was different from the occlusion treatment [32]. Taking together, it suggested that binocular fusion training, placing the images on corresponding areas in the two eyes, may provide a useful scaffold for integrating signals from the two eyes, and therefore present a more efficient way in recovery of stereovision in amblyopic patients [33]. It would be interesting to combine the different monocular and binocular therapy and verify if recovery of stereoaucuity and visual acuity are truly independent in further study.

There were several limitations in this study. The visual function of the majority of subjects still had deficits at the last follow-up visit. We are not clear whether there is regression in visual acuity when the treatment is stopped. In this pilot study, the sample sizes were roughly small. Large-scale, randomized, clinical trials are needed in the future. Additionally, this study did not involve all types of amblyopia, such as strabismus amblyopia, which was thought to have a greater degree of suppression than anisometropic amblyopia. Further study will focus on the efficacy of the AFG in both anisometropic and strabismus amblyopia.

**Conclusion**
In conclusion, AFG was a promising tool for treating anisometropic amblyopia, which could improve not only the monocular visual function but also the binocular visual function. Our results provided some insightful information for improving our understanding of the underlying suppression mechanism of anisometropic amblyopia and adding a new approach to the treatment strategy.

Acknowledgement

The authors thank Min Li for her valuable support during data collection.

Statement of Ethics

The study protocol complied with the requirements of the Institutional Review Board of Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine (IRB No. 2016KY229) and adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from the subjects and at least one of the subject’s legal guardians before participation. The trial registration number was NCT02970708, Registered 17 Nov. 2016.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author contributions

Study design: B.K. and Y.Y.; collection, management and interpretation of data: Y.Y., C.Z., P.W., X.H., W.Y., X.H. and B.K.; data analysis and writing of the article: Y.Y. and B.K.; preparation, review, and approval of the manuscript: Y.Y. and B.K.; Y.Y. contributed to the manuscript as the first author; B.K. contributed to the manuscript as the corresponding author. All authors read and approved the final manuscript.

References


Figure Legends

Fig. 1. The best corrected visual acuity at the baseline and each follow-up visit. Boxes indicate the mean value; whiskers represent the 95% confidence interval; *P < 0.05 compared with the baseline visual acuity in the AFG group; #P < 0.05 compared with the baseline in the patching group.

Fig. 2. The contrast sensitivity of the 3, 6, 12 and 18 cycles per degree spatial frequencies at the baseline and each follow-up visit (a. the patching group, b. the AFG group, boxes indicate the mean value).

Fig. 3. The improvement of contrast sensitivity function after 12-week treatment. Boxes indicate the quarters values (from 1/4 to 3/4 quarter); whiskers represent the maximum and minimum value; the hyphen in the box indicate the median value; the cross in the box indicate the mean value. *P < 0.05 compared with the improvement of contrast sensitivity function in the patching group.

Fig. 4. The stereoacuity at the baseline and each follow-up visit. Boxes indicate the mean value; whiskers represent the 95% confidence interval; *P < 0.05 compared with the baseline stereoacuity in the AFG group.
Table 1. The basic characteristics of the subjects.

<table>
<thead>
<tr>
<th></th>
<th>AFG group (N=20)</th>
<th>Patching group (N=20)</th>
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<tbody>
<tr>
<td>Gender (F/M)</td>
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<td>8/12</td>
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<tr>
<td>Age (years old)</td>
<td>10.00±2.13</td>
<td>9.05±2.09</td>
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<tr>
<td>SE (D)</td>
<td>3.43±2.21</td>
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<td>16.45±10.54</td>
</tr>
<tr>
<td>12 (dyl/deg)</td>
<td>5.85±7.72</td>
<td>7.20±7.00</td>
</tr>
<tr>
<td>18 (dyl/deg)</td>
<td>2.20±1.97</td>
<td>1.98±0.77</td>
</tr>
<tr>
<td>Stereoacuity (arc seconds)</td>
<td>609.00±860.54</td>
<td>576.00±637.15</td>
</tr>
</tbody>
</table>

SE: Spherical Equivalent, BCVA: best corrected visual acuity
Best corrected visual acuity (logMAR)

Follow-up visits

- Baseline
- 3w
- 12w

Patching vs AFG

* #