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A pilot randomized clinical trial of intermittent occlusion therapy liquid crystal glasses versus traditional patching for treatment of moderate unilateral amblyopia

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Abstract

Purpose

To compare the effectiveness of intermittent occlusion therapy (IO therapy) using liquid crystal glasses and continuous occlusion therapy using traditional adhesive patches for treating amblyopia.

Methods

Children 3-8 years of age with previously untreated, moderate, unilateral amblyopia (visual acuity of 20/40 to 20/100 in the amblyopic eye) were enrolled in this randomized controlled trial. Amblyopia was associated with strabismus, anisometropia, or both. All subjects had worn any optimal refractive correction for at least 12 weeks without improvement. Subjects were randomized into two treatment groups: a 4-hour IO therapy group with liquid crystal glasses (Amblyz), set at 30-second opaque/transparent intervals (occluded 50% of wear time), and a 2-hour continuous patching group (occluded 100% of wear time). For each patient, visual acuity was measured using ATS-HOTV before and after 12 weeks of treatment.

Results

Data from 34 patients were available for analysis. Amblyopic eye visual acuity improvement from baseline was 0.15 ± 0.12 logMAR (95% CI, 0.09-0.15) in the IO therapy group (n = 19) and 0.15 ± 0.11 logMAR (95% CI, 0.1-0.15) in the patching group (n = 15). In both groups improvement was significant, but the difference between groups was not (P = 0.73). No adverse effects were reported.

Conclusions

In this pilot study, IO therapy with liquid crystal glasses is not inferior to adhesive patching and is a promising alternative treatment for children 3-8 years of age with moderate amblyopia.

Conventional occlusion treatment for unilateral amblyopia in children has been occlusion with an adhesive eye patch, which forces use of the amblyopic eye while the nonamblyopic fellow eye is occluded. A landmark Pediatric Eye Disease Investigator Group (PEDIG) study showed that 2 hours' daily patching is effective in treating children 3-7 years of age with moderate, unilateral amblyopia (visual acuity, 20/40 to 20/80).[1,2] However, patching is not universally effective: 20% to 25% of children do not respond to treatment. Moreover, patching is disliked by patients and families,[3] and compliance has been found to be as low as 44%[4-7] to 57%,[8] limiting the potential visual acuity improvement significantly. Furthermore, the discomfort and social stigma of patching may cause stress or anxiety and adversely affect the child-parent relationship.[9,10] If the child's vision does not improve at an early age, it is increasingly difficult to achieve the optimal visual improvement later due to the limited critical period of vision plasticity. Therefore, investigating an effective alternative amblyopia treatment for young children is critical for long-term public health.

A novel electronic device, Amblyz liquid crystal intermittent occlusion glasses, alternates one lens between opaque and transparent phases at 30-second intervals so that they provide effective occlusion of one eye 50% of the time while worn. The intermittent occlusion therapy (IO therapy) associated with these glasses is potentially an effective alternative treatment for amblyopia for two reasons. First, cumulative occlusion time is critical for successful treatment. A positive and predominantly linear relationship between cumulative dose and response over at least the first 400 hours of amblyopia treatment has previously been reported.[11] Second, a recent study showed that splitting hours of patching is as effective as continuous hours of patching.[12] Although there is no evidence as to which interval duration or style is the best, it is reasonable to postulate that the IO therapy glasses may work at least as effectively as patching. Moreover, IO therapy glasses avoid adhesive and are more child friendly, potentially improving compliance. The feasibility and safety of this device in children has previously been confirmed.[13]

Two previous studies suggested that IO therapy could improve visual acuity in children with amblyopia.[14,15] Of note, neither study had a comparative patching control group; also, the occlusion dosage (total daily time of occlusion) varied among patients, depending on physician preference. Therefore, we do not know the true effectiveness of the IO therapy glasses when compared with patching.

Many US pediatric ophthalmologists currently follow PEDIG recommendation to prescribe 2 hours of patching for moderate amblyopia.[2,3,16,17] We hypothesized that 4 hours of IO therapy (50% of wear time) would not be inferior to 2 hours of traditional continuous adhesive patch occlusion in improving visual acuity in 3- to 8-year-olds with moderate, unilateral amblyopia. We tested our hypothesis with a 12-week randomized, controlled, noninferiority clinical trial using methods based upon the gold standard PEDIG Amblyopia Treatment Study (ATS) protocols for moderate amblyopia.

Subjects and Methods

This research protocol and the informed consent forms were approved by the Institutional Review Board of the Indiana University. Study oversight was provided by an independent data safety monitoring committee. Children 3 to ≤8 years of age with untreated, moderate, unilateral amblyopia, diagnosed and cared for by pediatric ophthalmologists at Indiana University School of Medicine were enrolled. Informed consent was obtained from the subject's parent or guardian (hereafter, "parent"); assent was obtained from 7- to 8-year-olds.

Eligibility testing included visual acuity in both eyes using the standard ATS single-surround HOTV letter protocol[18] and a routine comprehensive eye examination (cycloplegic refraction, comprehensive ocular examination, and a full motility examination). Inclusion and exclusion criteria are generally based on moderate amblyopia study criteria from the National Eye Institute (NEI).[1,2]

Subjects were eligible for inclusion if they met the following criteria: (1) age 3 to ≤8 years; (2) moderate unilateral amblyopia (best-corrected visual acuity in the amblyopic eye of from 20/40 to

20/100,[2] visual acuity in the sound eye of at least 20/40, and interocular logMAR difference of at least 2 lines); (3) amblyopia associated with strabismus, or anisometropia, or both; and (4) wearing of optimal spectacle correction (if needed) for a minimum of 12 weeks prior to enrollment. Details of the protocol for refractive correction for moderate amblyopia followed guidelines of a previous PEDIG study.[19] Exclusion criteria were as follows: (1) known allergy to adhesives.; (2) previous amblyopia treatment within 6 months of enrollment, except for optical correction; (3) gestational age of ≤32 weeks at birth; and (4) Down syndrome or developmental delays: (4) previous intraocular surgeries.

Each participant was randomly assigned to one of two treatment groups with a sealed envelope opened by the child or their parents: the IO therapy glasses intervention group (IO therapy group) or the standard patching control group (patching group). In the IO therapy group, the nonamblyopic fellow eye was treated with 4 hours' daily wear of 50% IO therapy glasses (Amblyz liquid crystal glasses, XPAND 3D Group, Ljubljana, Slovenia). Glasses were set at 30-second opaque/transparent intervals for the nonamblyopic eye (Figure 1). These glasses are rechargeable overnight, and after each charge the intermittent occlusion works for several days. The IO therapy glasses incorporate a snap-in carrier frame for individuals needing refractive correction with prescription lenses. In the patching group, the nonamblyopic eye received 2 hours' daily wear of standard, latex-free, adhesive patches combined with refractive correction (if needed).

To independently report compliance, all participants were provided with a calendar log, as used in previous patching treatment studies.[3,17] Once randomized, the patching group started their treatment immediately, whereas the IO therapy group typically started treatment 6-10 days after randomization due to the delay of acquiring the optical correction insert for the IO therapy glasses. In cases of accidental breakage of IO therapy glasses, the patient received a replacement pair of glasses within 1 week.

After a 12 weeks of treatment, each participant returned for his or her routine eye examination

and best-corrected ATS-HOTV visual acuity was measured by a certified examiner who was masked to the patient's treatment. Ocular alignment was measured using the simultaneous prism and cover test at distance and near. Compliance was evaluated based on the calendar log and was defined as the percentage of actual eye patch or IO therapy glasses wear hours versus the total prescribed patching or IO therapy glasses wear hours.[5,20] The participant's parent was asked to comment about their child's treatment experiences.

We monitored for potential major adverse events, including reverse amblyopia (visual acuity in the sound eye decrease by 2 lines) in the nonamblyopic eye, significant changes in ocular alignment (deviation changes of $\geq 10^{\Delta}$), skin irritation from the patches, and injury associated with the liquid crystal glasses and possible breakage.

Statistical Analysis

The primary outcome was the visual acuity change in the amblyopic eye (logMAR) at the 12-week primary outcome visit. A paired *t* test was applied to analyze visual acuities before and after treatment for each group; an independent *t* test was applied to analyze visual acuity improvement between groups. Confidence intervals of visual acuity improvement are reported in a noninferiority manner.[21] After intervention type was considered, correlation coefficients were calculated for the treatment response (improved visual acuity in the amblyopic eye) to the variables: (1) baseline visual acuity; (2) severity of amblyopia; and (3) subject age.

A sample size of 12 subjects per group has been shown to be effective for estimating within-group means and variances when little prior data is available.[22] Although a number of 12 would work for a pilot study, we overestimated the sample size to 20 in each group to account for attrition because we were uncertain how many participants would drop from the study. Based on collected data from 34 subjects and effective size difference of 0.1, we reestimated this study as a noninferiority trial with continuous outcome and power calculated as approximately 80%.

Results

Between January 2014 and August 2015, 49 patients were consented; 45 entered the trial, with 27 assigned to the IO therapy group and 18 to the patching group (Figure 2). We planned to enroll patients at 4 clinics. Randomized group assignments were distributed in sealed envelopes. Although we expected equal number of patients assigned to each treatment with randomization, uneven numbers were enrolled into the two arms because we did not randomize in blocks for each clinic site and two of the four clinics did not enroll any patients.

Following the intent-to-treat strategy, the 12-week outcome examination was completed by 19 of the patients in the IO therapy group and 15 patients in the patching group. Of the 34 included subjects, 28 (82%) were white. The baseline characteristics of the patients in both groups were similar (Table 1). There were more boys in the IO therapy group than in the patching group. The baseline visual acuity was on average 0.46 logMAR (approximately 20/58) for both groups.

Visual Acuity Improvement in the Amblyopic Eye

At 12 weeks of treatment, visual acuity in the amblyopic eye improved an average (with standard deviation) of 0.15 ± 0.12 logMAR (95% CI, 0.09-0.15) in the IO therapy group and 0.15 ± 0.11 (95% CI, 0.10-0.15) logMAR in the patching group. The window for the primary outcome visit was ±1.5 weeks. The individual and mean in the amblyopic eye is plotted in Figures 3 and 4. The visual acuity improvement in two groups was not statistically significant ($t = -0.14$ [independent t test], one-sided $P = 0.88$; Figure 3), indicating that the IO therapy was not inferior to patching. In the IO therapy group 4 patients improved by 3 lines and 3 patients did not improve; similarly, in the patching group 4 patients improved 3 lines and 3 patients did not improve (Figure 4).

One subject in each group reported not having applied any treatment; therefore, we performed a secondary analysis excluding these 2 patients. At 12 weeks, visual acuity in the amblyopic eye improved an average of 0.15 ± 0.12 logMAR (95% CI, 0.09-0.15) in the IO therapy group (n = 18) and

0.16 ± 0.11 (95% CI, 0.1-0.16) logMAR in the patching group (n = 14). The difference between groups was not statistically significant ($t = -0.34$ [independent t test], one-sided $P = 0.37$). In this secondary analysis**,** 4 patients improved by 3 lines and 3 patients did not improve in the IO therapy group; 4 improved by 3 lines and 2 did not improve in the patching group.

Severity of Amblyopia

At baseline, severity of amblyopia was 0.39 ± 0.12 logMAR in the IO therapy group and 0.35 ± 0.12 logMAR in the patching group. At 12 weeks, severity of amblyopia was 0.28 ± 0.19 logMAR in the IO therapy group and 0.23 ± 0.13 logMAR in the patching group. This decrease in the severity of amblyopia was significant in both groups (IO therapy group, $t = 3.19$, $P = 0.005$; patching group, $t = 3.81$, $P = 0.002$ [paired t test]). The difference in the decrease of severity between groups was not significant ($t = 1.00$; $P = 0.32$).

Correlation with Baseline Visual Acuity, Severity of Amblyopia, Treatment Age

In the IO therapy group, the correlation coefficient of the improved visual acuity in the amblyopic eye with baseline visual acuity was 0.05 ($P = 0.83$); with severity of amblyopia, −0.02 ($P = 0.94$); and with treatment age were, −0.03 ($P = 0.90$). In the patching group, the correlation coefficients were 0.21 ($P = 0.45$), 0.41 ($P = 0.13$), and −0.07 ($P = 0.80$), respectively. No significant correlation was found.

Effect of Treatment on the Nonamblyopic Fellow Eye

At baseline, mean visual acuity of the *nonamblyopic* eye was 0.07 ± 0.13 logMAR in the IO therapy group and 0.11 ± 0.09 logMAR in the patching group ($t = -0.86$ [independent t test], $P = 0.40$). At the 12-week visit, mean visual acuity in the *nonamblyopic* eye was 0.03 ± 0.11 logMAR in the IO therapy group and 0.08 ± 0.12 logMAR in the patching group ($t = -1.23$ [independent t test], $P = 0.23$). At both baseline and 12-week visits, the two groups have no significant difference. No patients in either group had reverse amblyopia.

Strabismus

No patients in either group had a significant increase in strabismus (defined as 10^{Δ} of increase at either near or distance).

Compliance

Compliance was reported by 8 patients in the IO therapy group and 10 patients in the patching group; compliance averaged at 92% in the patching group and 84% in the IO therapy group. This difference was not statistically different ($P = 0.38$ [independent t test]).

Patients/Parents Comments on IO therapy glasses

Generally, the comments demonstrated a high level of enthusiasm from parents and children with the IO therapy glasses, commonly remarking that they were easy to wear for the prescribed treatment time. Children often struggled with some outdoor activities but reported no issues with indoor activities while occluded; some parents reported that their child had trouble seeing outside at night; some parents complained that the glasses were easily damaged. Several patients complained that the glasses were variably tight, loose, or uncomfortable, often due to the nose pad or temple arm. For most of these complaints, our opticians were able to successfully adjust the glasses to fit the child or offer a spectacle elastic band; but, in 2 patients, these adjustments did not satisfactorily resolve the complaint, and they did not wear the glasses as directed because of the uncomfortable glasses. One patient reported a "rainbow effect" when using a pair of IO therapy glasses, but this complaint resolved when the glasses were replaced with a new pair. Overall, there were no adverse effects or injuries reported in this study. No skin irritation was reported in the patching group.

Discussion

This pilot study is the first randomized clinical trial to compare the effectiveness of liquid crystal occlusion glasses and adhesive occlusion patches in children 3-8 years of age with moderate unilateral amblyopia. It is also the first hypothesis-based study to compare intermittent occlusion with continuous occlusion. The results suggest that 4 hours of intermittent occlusion is not inferior to 2-hours of

continuous occlusion in treating moderate amblyopia.

Table 2 highlights how our study differs from two previous studies with liquid crystal glasses.[14,15] First, we studied only moderate amblyopia, which is similar to Spierer and colleauges,[14] whereas Erbagci and colleagues[15] included both severe and moderate amblyopia in their 14 patients. Visual acuity improvement in our study is similar to the results at 3 months in Spierer and colleagues,[14] although our daily dosage were less. Conversely, visual acuity improvement in Erbagci and colleagues[15] was greater than ours. The most likely explanation for this difference is that their patients did not have a refractive adaptation period, and many patients with amblyopia show significant improvement in visual acuity using optical correction alone.[15]

Second, the daily dosage in our study is relatively brief. Based on our hypothesis, we designed our study with 4 hours of IO therapy to achieve the 2 hours of daily occlusion. In both previous studies, IO therapy hours were not fixed and prescribed amounts were left to the individual physicians' preference, which varied from 4 to 12 hours.[14,15]

Third, our study is the only one to report severity of amblyopia. We reported this calculation because rapidly developing children at 3-8 years of age could experience improvement in visual acuity solely or in part through physical development rather than from the treatment itself. Such a developmental improvement in visual acuity would be reflected in improved vision in *both* eyes, not just the amblyopic eye.

Experiences with IO Therapy Glasses

The current version of IO therapy glasses is "one size fits all." As a result, we had to exclude several children from enrollment whom the glasses did not fit appropriately. This device may be improved in the future with additional frame sizes. As with all glasses worn by children, there was some breakage, but nothing seemed out of the ordinary, and there were no injuries related to the glasses. Although some local Amish parents declined to participate in the study because of the electronic nature of the

glasses, children and families were typically enthusiastic about using the "high tech" glasses and voiced no concerns about the sports-goggle type frames.

Compliance in both groups was similar, despite the fact that the daily wearing hours were doubled for the IO therapy group. We recognize that self-reported compliance is often overestimated compared to objective compliance, however, both groups used the same compliance reporting system and we found no significant difference between groups.[23]

Several patients did not keep the scheduled 12-week visit. Additionally, some children who performed well at enrollment subsequently did not cooperate during 12-week visual acuity testing. Therefore, the sample size decreased from 49 to 34. However, based on available data from the sample size obtained, the power of this study as a noninferiority trial was calculated as approximately 80%. Thus, this study was adequately powered.

In 2014 the FDA approved Amblyz IO therapy glasses as a medical device (but not as a specific therapy for amblyopia). Until now, clinicians had no evidence-based guidelines for prescribing these glasses. Besides providing such evidence, this study suggests that it may be the cumulative time of occlusion is important rather than the daily dosage. This finding may make it easier to occlude individuals, who frequently do not tolerate patching.

This pilot study suggests that, at 12 weeks of treatment, 4 hours' daily IO therapy with liquid crystal glasses set at 50% occlusion time was not inferior to 2 hours' daily patching in treating children 3-8 years of age with moderate, unilateral amblyopia. This promising IO therapy provides an alternative form of amblyopia treatment for children. These results support further study with a multicenter, randomized clinical trial to confirm our findings and delineate baseline factors that may influence the effectiveness of IO therapy glasses versus patching, such as age, severity of amblyopia and sub-type causes of amblyopia.

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Legends

FIG 1. IO therapy glasses with the liquid crystal glasses in the occlusive, opaque mode (top) and in their natural state (bottom).

FIG 2. Flow diagram of patients' enrollment and follow-up.

FIG 3. Visual acuities in individuals at the baseline and at 12-week follow-up for the IO therapy group (A) and the patching group (B); means at baseline and 12-week follow-up were plotted.

FIG 4. Mean visual acuity improvement for both groups at 12-week outcome visit. Both groups improved significantly from the baseline and there is no significant difference between the groups.

Table 1. Baseline characteristics according to treatment group

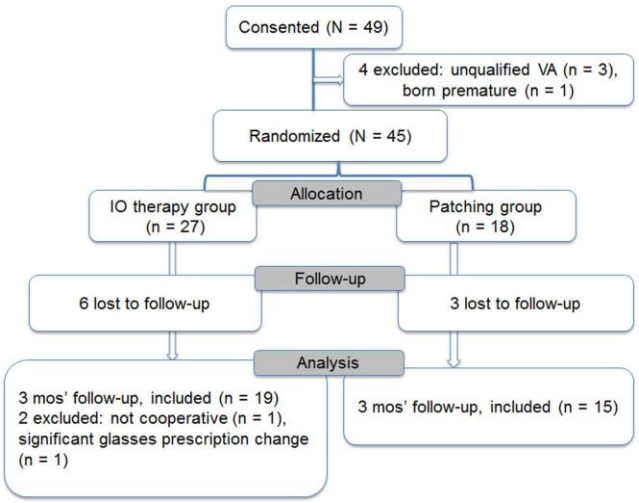
Characteristic	Total (N = 34)	IO therapy group (N =19)	Patching group (N = 15)
Sex (F/M)	12/22	5/14	7/8
Age, years	5.8±1.2	5.7±1.5	5.9±0.9
3-4	2	2	0
4-5	8	5	3
5-6	7	4	3
6-7	13	4	9
7-8	4	4	0
Cause of amblyopia			
Strabismus	12	9	3
Anisometropia	20	8	12
Combined strabismus + anisometropia	2	2	0
VA in the amblyopic eye at baseline, logMAR	0.46 ± 0.13	0.46 ± 0.16	0.46 ± 0.14
Severity of amblyopia or interocular difference of VA at baseline, logMAR	0.39 ± 0.12	0.35 ± 0.12	0.38 ± 0.14

logMAR, logarithm of the minimum angle of resolution; *VA*, visual acuity.

Table 2. Comparison with prior IO therapy studies

	Spierer et al (2010)[14]	Erbagci et al (2015)[15]	Our study
Control group	No	No	Yes
Sample size	24	14	19 (IO therapy), 15 (patching)
Age at treatment, years	4-7.8	4.5-10	3-8
Patient characteristics	Moderate amblyopia; previously treated or untreated	Moderate and severe amblyopia; previously untreated; no optical correction adaptation period	Moderate amblyopia; previously untreated; optical correction adapted
IO therapy glasses occlusion setting	40 seconds on and 20 seconds off	30 seconds on and 30 seconds off	30 seconds on and 30 seconds off
Daily IO therapy hours	At least 8 hours	4-12 hours	4 hours
Reported follow-up period, months	1.5, 3, 4.5, 6, 9	3-7 (mean, 4.0 ± 1.2)	3
Visual acuity improvement, logMAR	0.16 ± 0.3 (at 3 months)	0.3 ± 0.2	0.15 ± 0.12

LogMAR, logarithm of the minimal angle of resolution.



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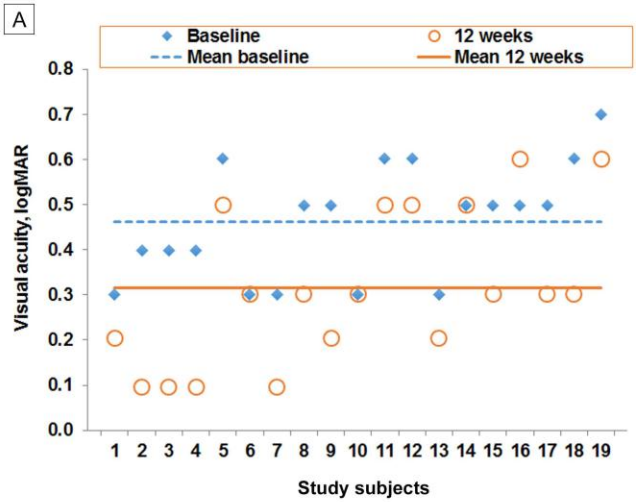

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