Feasibility of monitoring compliance with intermittent occlusion therapy glasses for amblyopia treatment

Jingyun Wang, PhD,[a] Jing Jin MD, PhD,[b,c] Ayesha Malik, OD,[d] Ruth Shoge, OD,[a] Siva Meiyeppen, OD,[a] Yi Pang, OD, PhD,[e] Kelly Yin, OD,[e] Megan Allen, OD,[e] Brandy Scombordi, OD,[a] Ajay Soni, MD,[f] Daniel E. Neely, MD,[g] and Kai Januschowski MD[h,i]

Author affiliations: [a]Salus Univerisity, Elkins Park, Pennsylvania; [b]Nemours/Alfred I. duPont Hospital for Children, Wilmington, Delaware; [c]Wills Eye Hospital, Philadelphia, Pennsylvania; [d]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [e]Illinois College of Optometry, Chicago, Illinois; [f]Penn State Eye Center, Hershey, Pennsylvania; [g]Glick Eye Institute, Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana; [h]Eye Clinic Sulzbach, Sulzbach/Saar, Germany; [i]Department for Ophthalmology, Eberhard Karls University Tuebingen, Germany

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Correspondence: Jingyun Wang, PhD, Salus University, Pennsylvania College of Optometry, 8360 Old York Rd, Elkins Park, PA 19027 (email: jwang@salus.edu).

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Abstract

Background

Liquid crystal glasses use an intermittent occlusion technique and may improve compliance compared to adhesive patches. Previous studies support the effectiveness of intermittent occlusion therapy (IO therapy) glasses for amblyopia treatment. However, objective compliance for these glasses has not been measured. The purpose of this study was to investigate the feasibility of using a microsensor to monitor objective compliance with IO therapy glasses.

Methods

Children 3 to ≤8 years of age with unilateral amblyopia were enrolled. All subjects had optimal refractive correction (if needed) for at least 5 weeks without improvement. Subjects were prescribed IO therapy glasses, set at 30-second opaque/transparent intervals (ie, occluded 50% of wear time). Wear time was prescribed according to amblyopia severity. For each patient, objective compliance with the IO therapy glasses was monitored by means of a microsensor.

Results

A total of 13 subjects returned with microsensor data. Compliance varied among and within individuals. General compliance averaged 51.6% (range, 10%-97%). Mean daily compliance decreased slightly over time. On average, patients' visual acuity improved 0.14 ± 0.15 logMAR (range, −0.1 to 0.5 logMAR). No parents reported that their child had social concerns related to the attached microsensor.

Conclusions

Objective compliance with IO therapy glasses can be monitored by a simple microsensor reliably. In our study cohort, objective compliance with IO therapy glasses varied among individuals, but on average it declined slightly over time.

For amblyopia treatment, intermittent occlusion (IO) therapy enabled by liquid crystal technology glasses presents an alternative to patching. IO therapy glasses can be programmed to unilaterally alternate between opaque and transparent phases at 30-second intervals, providing effective occlusion of fellow eye 50% of the time they are worn. Previous studies have assessed the effectiveness of the IO therapy glasses.[1-3] Because the glasses are child friendly, they can potentially improve compliance with occlusion.

Previous studies have prescribed IO therapy glasses to patients with amblyopia for different treatment hours. Spierer and colleagues[1] used IO therapy glasses with a 2:1 occlusion/transparent ratio, prescribed at least 8 hours to children with moderate amblyopia, an equivalent of "at least 5.3 hours occlusion per day." Erbagci and colleagues[2] described IO therapy glasses with a 1:1 occlusion/transparent ratio (prescribed at least 4-12 hours to children with moderate and severe amblyopia) as effectively resulting in 2-6 hours occlusion per day. Wang and colleagues[3] hypothesized that 4 hours of IO therapy would equal 2 hours of patching and, for IO therapy glasses with 1:1 occlusion/transparent ratio, prescribed 4 hours to children with moderate amblyopia. All of these studies described a benefit of IO therapy; however, there is no consensus with regard to how much IO therapy is needed to effectively treat amblyopia. Nor have previous studies objectively measured compliance with glasses wear, limiting reliable assessment of the dose–response relationship of IO therapy. Spierer and colleagues[1] and Erbagci and colleagues[2] estimated a high degree of compliance with prescribed use of IO therapy glasses. In the study of Wang and colleagues,[3] however, all participants were provided with a calendar log to independently report compliance, which has been used in previous patching or atropine amblyopia treatment studies.[4,5] They reported that the self-reported compliance with IO therapy

is similar to that of patching, in lieu of the expected higher compliance.[3] Objective data on compliance with IO therapy glasses is lacking.

Januschowski and colleagues[6] previously used microsensors on common spectacles to monitor glasses wear. IO therapy glasses differ from common spectacles because the dosage of IO therapy may vary with periodic treatment outcome, and cumulative occlusion time is critical for successful treatment.[7] Finding an efficient method for monitoring compliance is critical for both research and clinical results. The purpose of the present study was to evaluate the feasibility of using a microsensor to monitor compliance with IO therapy glasses in children 3 to ≤8 years of age with unilateral amblyopia.

Subjects and Methods

This research protocol and the informed consent forms were approved by the Salus University Institutional Review Board and complied with the US Health Insurance Portability and Accountability Act of 1996. Children 3 to ≤8 years of age with unilateral amblyopia from eye clinics in the greater Philadelphia and Chicago areas were enrolled. Informed consent was obtained from the subject's parent or guardian (hereafter, "parent"); assent was also obtained from subjects 7-8 years of age. Eligibility testing included measurement of visual acuity in both eyes using the standard ATS single-surround HOTV letter protocol[8] and a routine comprehensive eye examination (comprehensive ocular examination and a full motility examination). Cycloplegic refraction was completed within 6 months. Children were eligible for inclusion if they met the following criteria: age 3 to ≤8 years; unilateral amblyopia, that is, best-corrected visual acuity of the amblyopic eye ranging from 20/40 to 20/400[9]; interocular logMAR difference of at least 2 lines; visual acuity in the sound eye of at least 20/40 or better; amblyopia associated with strabismus, anisometropia, or both, or with post-cataract surgery; wearing of

optimal spectacle correction (if needed) for a minimum of 5 weeks prior to enrollment; and amblyopic eye either untreated by patching or atropine for at least 6 months. Subjects were not included if they had a known allergy to adhesives; gestational age of ≤32 weeks at birth; or Down syndrome or developmental delays.

Details of the protocol for correction of refractive error followed previous PEDIG amblyopia treatment study guidelines.[10] In brief, hyperopia was not undercorrected by more than +1.50 D spherical equivalent, and undercorrection in plus was symmetric in both eyes; cylinder power in both eyes was within 0.50 D of fully correcting the astigmatism; cylinder axis in both eyes was within 6° of the axis of the cycloplegic refraction; and spherical equivalent was within 0.50 D of fully correcting the anisometropia.

Each participant was provided a pair of rechargeable IO therapy glasses (Amblyz liquid crystal glasses; XPAND 3D Group, Limassol, Cyprus) with the proper prescription. Glasses were set at 30-second opaque/transparent intervals for the nonamblyopic fellow eye (Figure 1A).

To independently monitor compliance, IO therapy glasses were provided with a TheraMon microsensor (Hargelsberg, Austria).[6] It is inexpensive and commercially available. The microsensor is 9 × 13 mm in size, encapsulated in polyurethane, and waterproof. It does not cause skin irritation and carries no significant risk. The preset “headgear” software option allowed for external use. The microsensor was glued to the temple arm to enable detection of threshold temperature (Figures 1B-C). When the child wore the glasses, the microsensor was in direct contact with the skin and recorded body temperature every 15 minutes. During a routine visit, the stored data was downloaded at a reading station for analysis.[6] The microsensor recorded all temperatures after initiation. The threshold temperature of 82°-96° F was the same for every child. Generally, the temperature graph shows a sudden increase of temperature when the device

is first worn and a sharp drop of temperature when it is removed, which was always possible to distinguish. A sudden increase in temperature close to the body temperature was defined as the starting point of the wear time; a sudden drop, as the end point.[6] The period between start and end was counted as "wear" time.

Participants were from two clinical trials. For clinical trial NCT02687581, patients with severe amblyopia who failed patching were prescribed with 12-hour IO therapy for 12 weeks. For clinical trial NCT02767856, patients with moderate amblyopia were randomized with 12-hour IO therapy for 4 weeks or 4-hour IO therapy for 12 weeks.

After a 4- or 12-week period of treatment, each participant returned for a routine follow-up eye examination. Compliance was evaluated based on recorded wear data: compliance was defined as the percentage of hours glasses were worn compared to hours of wearing prescribed. Daily compliance was calculated, and general compliance was determined as the average of daily compliance for individuals. The correlation of age and compliance was calculated. Descriptive statistics was applied. Daily compliance was fit with linear regression. In addition, we compared mean objective compliance with IO therapy with patching results of Wallace and colleagues.[11]

The participant's parent was asked to comment about their child's experiences with IO therapy glasses. Potential major adverse events monitored for included any injury associated with IO therapy glasses or the microsensor. Any loss or possible breakage was recorded.

Results

Between June 2016 and April 2018, 20 patients were enrolled, of whom 13 returned with microsensor data for analysis. Table 1 provides the basic characteristics of these patients.

In this study, the longest period of monitoring IO therapy glasses with the mircosensor was about 48 weeks (approximately 9 months). Figure 2A shows an example of a patient's daily

compliance with IO therapy over 48 weeks as recorded by one microsensor. Figure 2B shows an example of patient's daily compliance with IO therapy over 12 weeks. Compliance varied among and within individuals. Figure 3 shows the mean compliance with IO therapy over 12 weeks. General compliance over 4 weeks was averaged at 51.6% (range, 10%-97%). Compliance varied among individuals, and variances were significant. Over the 3-month follow-up period, mean daily compliance declined slightly with time.

Three of 13 patients had broken glasses over the treatment duration. In such cases, we immediately shipped them a new pair of glasses with a new microsensor, and the glasses arrived within one week. One patient's parent reported that the microsensor dropped off, and the parent reattached it himself with superglue with our instruction. No parent reported that their children had social concerns related to the attached sensor or IO therapy glasses.

Over 4-12 weeks, patients' visual acuity improved on average 0.14 ± 0.15 logMAR (range, −0.1 to 0.5 logMAR).

Discussion

This is the first study to monitor compliance with IO therapy using a microsensor affixed to glasses in patients 3 to ≤8 years old with unilateral amblyopia. Compliance with IO therapy was not as high as we expected and varied greatly from patient to patient. Our results suggest that treatment guidelines and data from existing studies regarding IO therapy should be regarded critically. We also recommend that compliance measurements should be included in future research studies and clinical practice.

Wang and colleagues[3] showed that IO therapy is as effective as patching occlusion therapy in children with moderate amblyopia. The relative ease of use with IO therapy possibly leading to better compliance compared with patching was discussed. This was not supported by

the findings in our study.[3] It seems that the occlusion of the fellow eye per se or the cosmetic factor associated with occlusion were the major factors influencing compliance, independent of the occlusion method. We do note, however, that decreasing adherence over time seems to be less accentuated in IO therapy subjects. This needs to be elaborated on in future studies. One limitation of the current study is that we compared our data to compliance with patching from Wallace and colleagues[11] rather than a concurrent randomized control group. And although we did incorporate some aspects of the PEDIG protocol into our study design (eg, spectacle correction criteria), there remain differences in the inclusion criteria for the two studies. As a result, we must be cautious in interpreting the comparison.

It could also be argued that the IO therapy glasses were only worn during the occlusion phases, possibly negatively affecting compliance. Adhering to the prescription of certain hours per day requires switching between IO therapy glasses and spectacles; this switch added some novel challenges for compliance. This might be improved by technical developments, for example, occlusion glasses that can be worn all day for refractive correction and only shutter during certain periods of time.

One advantage of the microsensor is its ability to store data for up to 100 days. We scheduled 1-month or 3-month follow-up visits for our patients after amblyopia treatment was initiated. Other previous amblyopia compliance studies[12,13] used monitors that had a short battery life, and patients had to return after a short time period. For example, Maconachie and colleagues[13] used a glasses dose monitor to investigate compliance with glasses in children with amblyopia. The device cannot monitor each patient over an extended period of time. Each patient needed 4-5 glasses dose monitors for a 6-week study, which required very frequent visits. Tjiam and colleagues[12] used an occlusion dose monitor, which had a battery life of around 1 week.

More frequent visits to the ophthalmologist may result in higher compliance, and compliance is significantly higher for those patients who had frequent visits.[11] Compared with previous reports, compliance measured with the microsensor in this study may reflect actual clinical compliance more accurately.

One concern related to compliance with IO therapy glasses is whether the patient wore spectacles before IO therapy. All patients in this study wore spectacles before they were treated with IO therapy glasses. Maconachie and colleagues[13] found that compliance with spectacle wear is less than optimal, and high compliance with spectacle wear is highly associated with later patching compliance. Similarly, we may hypothesize that compliance with IO therapy glasses is related to previous spectacle wear. In this study, 3 of 13 patients had broken glasses, and 1 patient reported that the microsensor dropped off. These events indicate that a reliable compliance report by the microsensor depends on the quality of the IO therapy glasses.

It is possible that compliance was underestimated in our study. The microsensor samples every 15 minutes, which means that it could have not recorded 15 minutes of compliance when the child transitioned from wear to nonwear, or nonwear to wear, of the IO therapy glasses. On average, we can factor in 15 minutes of underestimation. For example, if we assume one does not take off the glasses during the prescribed duration, then, for a 4-hour treatment, underestimation could be 15 minutes / (4 hours * 60 minutes per hour) = 2%. For a 12-hour treatment, underestimation could be 15 minutes / (12 hours * 60 minutes per hour) = 0.3%. The underestimation may multiply with glasses-taking-off times (n + 1). Therefore, the underestimation could be 15 minutes * (n + 1) / (prescribed hours * 60). For example, for a 4-hour treatment in which the glasses are removed 2 times, underestimation could be 15 minutes * (2+1) / (4 hours * 60 minutes per hour) = 6%. The more the patient takes off the glasses, the

more we would underestimate compliance. It may be advisable for future studies to change the recording intervals, especially during shorter application times.

Of course, if children looked over the IO therapy glasses while wearing them, the microsensor would still record compliance. The IO therapy glasses are relatively small and tight-fitting, however, and patients cannot easily look over them. Finally, the microsensor has limitations with ambient temperature. Any reading within the threshold temperature range was considered "wear." Therefore, the microsensor lost accuracy if surrounding temperature is between 33 and 37°C (91°-99° F).[6] The similar limitation (91°-99° F) was reported for the previous occlusion-dosage monitor.[14,15] Temperatures in this range were uncommon in the northeastern United States during the period of the study, but it is still a potential confounder. Schramm and colleagues[16] reported the microsensor can reliably distinguish if the sensor is worn when it touches the skin or if it is in the trouser pocket. Despite the limitations of our study, we are optimistic that monitoring glasses wear in IO therapy will lead to better understanding of compliance patterns in our patients and to approaches to enhance compliance and thus improve amblyopia treatment.

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Legends

FIG 1. A, Intermittent occlusion (IO) therapy glasses. B, Microsensor attached to left temple. C, Magnified view of microsensor.

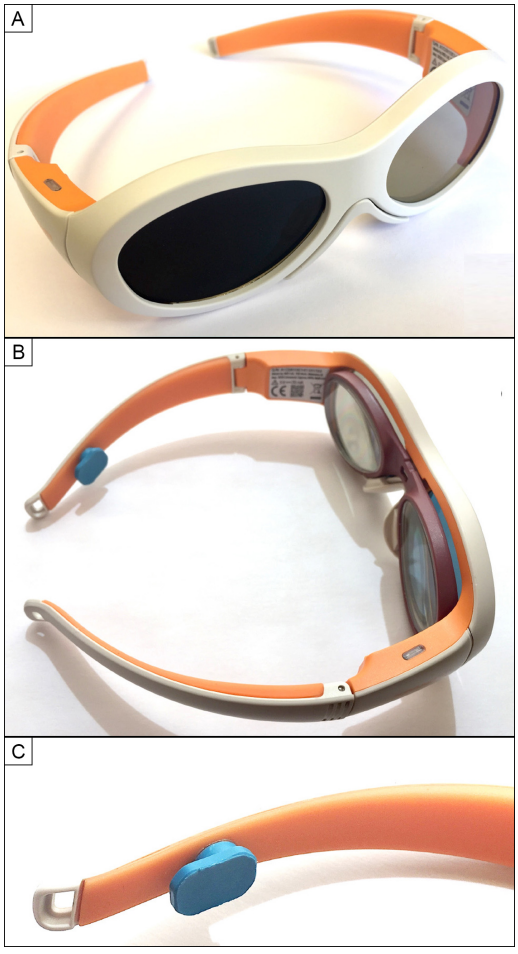
FIG 2. A, Microsensor compliance report from a 7.5-year-old boy (patient 7) who wore IO therapy glasses for over 9 months. This child wore a single sensor for 3 12-week follow-up visits; his compliance slightly decreased over time. B. Example of a microsensor compliance report from a 5.5-year-old boy (patient 9) who wore IO therapy glasses for 12 weeks; his compliance was relatively consistent after the first 10 days.

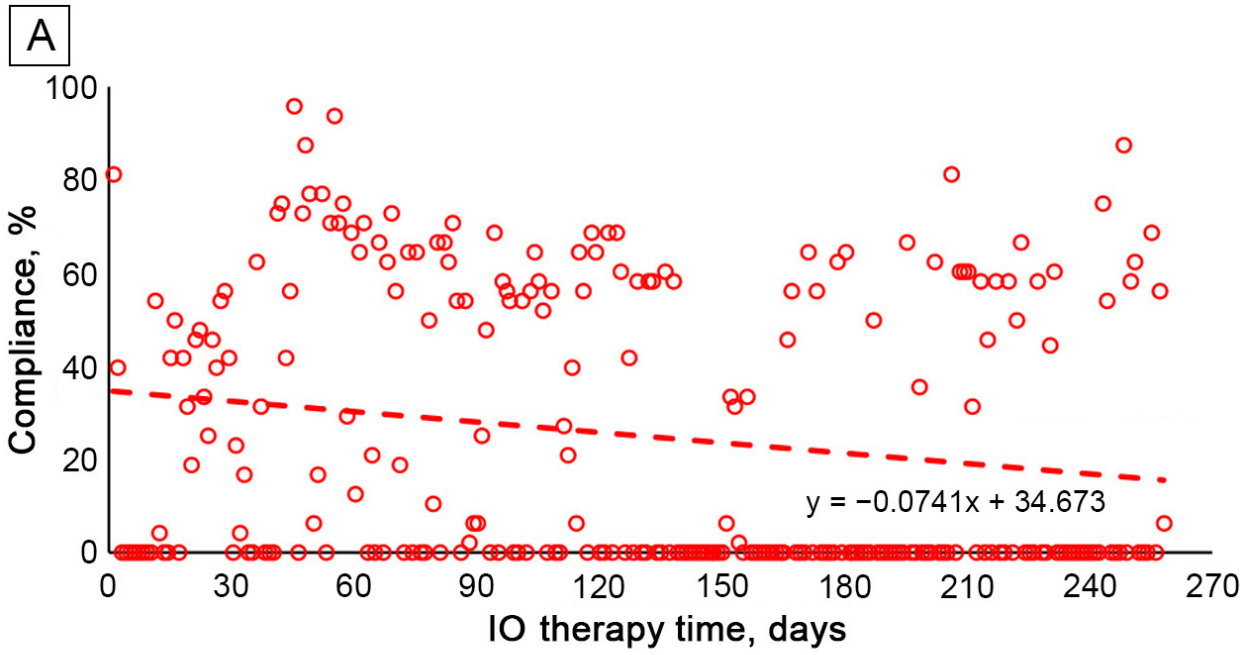
FIG 3. The mean daily compliance over 12 weeks was fitted with linear regression. It is compared with the mean patching compliance in green from Wallace and colleagues.[11] Error bars indicate standard deviation.

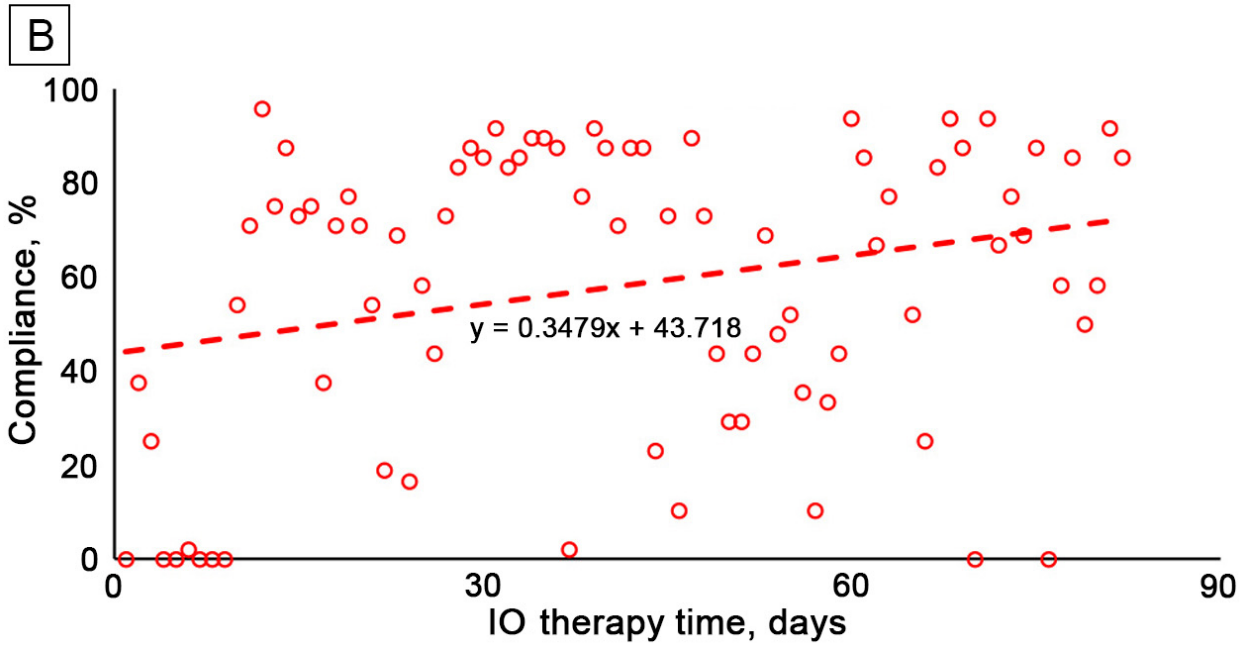
Table 1. Basic characteristics and general compliance for the first 4 weeks

				Visual acuity, logMAR			
Patient	Age, years	Sex	Amblyopia type	Amblyopic eye	Fellow eye	Severity of amblyopia	4-week general compliance, %
1	7.2	M	Strabismic	0.6	0.2	0.4	16
2	4.5	M	Strabismic	0.9	0.0	0.9	10
3	7.1	F	Deprivation	0.5	−0.1	0.6	97
4	7.1	F	Anisometropic	0.4	−0.1	0.5	48
5	5.2	M	Anisometropic	0.5	0.2	0.3	71
6	6.6	F	Anisometropic	0.4	0.1	0.3	90
7	4.1	F	Strabismic	0.3	0.1	0.2	40
8	7.6	M	Anisometropic	0.9	−0.1	1.0	27
9	5.9	M	Anisometropic	0.3	0.1	0.2	79
10	5.5	M	Anisometropic	0.7	0.2	0.5	48
11	7.6	M	Anisometropic	0.3	0.1	0.2	85
12	6.5	M	Anisometropic	0.6	0.1	0.5	26
13	6.2	F	Strabismic	0.4	0.1	0.3	39
Mean ± SD	6.24 ± 1.14			0.5 ± 0.2	0.1 ± 0.1	0.5 ± 0.3	51.6 ± 29.7

SD, standard deviation; *VA*, visual acuity.




A
Compliance, %
100
80
60
40
20
0
0
30
60
90
120
150
180
210
240
270
IO therapy time, days
y = −0.0741x + 34.673


B
Compliance, %
100
80
60
40
20
0
0
30
60
90
IO therapy time, days
y = 0.3479x + 43.718