

Objectively-measured compliance to atropine penalization treatment in children with amblyopia: a pilot study

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Background: To date, compliance to atropine penalization in amblyopic children has only been assessed through self-report. The goal of this pilot study is to measure compliance to atropine penalization objectively.

Methods: Seven amblyopic children (3–8 years; 20/40–20/125 in the amblyopic eye) were enrolled. None had been treated with atropine previously. Children were prescribed either a twice per week or daily atropine regimen by their physicians. Compliance was defined as the percentage of days in which the atropine eye drop was taken compared to the number of doses prescribed. We used medication event monitoring system (MEMS) caps to objectively measure compliance. The MEMS caps are designed to electronically record the time and date when the bottle is opened. The parents of the children were provided a calendar log to subjectively report compliance. Participants were scheduled for return visits at 4 and 12 weeks. Weekly compliance was analyzed.

Results: At 4 weeks, objective compliance averaged 88% (range, 57–100%), while subjective compliance was 98% (range, 90–100%). The actual dose in grams and visual acuity (VA) response relationship ($r=0.79$, $P=0.03$) was significantly better than the relationship between regimen and response ($r=0.41$, $P>0.05$), or the relationship between actual dose in drops and response ($r=0.52$, $P>0.05$).

Conclusions: Objective compliance to atropine penalization instructions can be monitored with MEMS, which may facilitate our understanding of the dose-response relationship. Objective compliance with atropine penalization decreases over time and varies with regimen. On average, subjective parental reporting of compliance is overestimated.

Keywords: Atropine penalization; amblyopia treatment; compliance

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Introduction

Unilateral amblyopia or “lazy eye” is the most common cause of monocular visual impairment with an estimated prevalence of 2–5% in children and young and middle-aged adults (1,2). Currently, two main approaches, patching and atropine penalization, are used to treat amblyopia.

The goal of both methods is to force the amblyopic eye to work “harder”. Patching requires the children to occlude their fellow eye with an adhesive patch for 2–6 hours per day, while atropine penalization uses an atropine eye drop to blur vision in the fellow eye. The success of atropine penalization for amblyopia treatment has been well established (3–6). For example, the effect of atropine on

amblyopia at 6-month follow-up was shown to be similar to patching treatment (7). Also, during a follow-up at the age of 10 years, atropine treatment effects achieved before 7 years of age were maintained (8).

As a simpler approach, atropine treatment appears to be more favorable or popular to the child and family than patching (9,10). Subjective compliance, or self-report compliance, to atropine penalization treatment has been reported in a few Pediatric Eye Disease Investigator Group (PEDIG) studies, where it ranges from 59% to 94% (3,5,6). Although subjective compliance to both atropine and patching approaches shows considerable between-patient variability, compliance to the atropine penalization treatment is generally higher than subjective compliance to patching treatment (3,5,6).

The higher compliance to the atropine penalization treatment has been attributed to several factors, including the greater ease of management for parents compared to patching. It is also less disruptive to the child's daily life than traditional hours of patching and is associated with lower psychosocial or cosmetic issues. In addition, since the cycloplegic effect of topical atropine usually lasts for several days, imperfect compliance with atropine may not impact the treatment as much as imperfect compliance with patching.

However, atropine penalization has some disadvantages that may adversely affect patient compliance and a more thorough investigation of compliance is warranted, particularly in light of the large variability in the reported rates of compliance. For example, as a pharmaceutical, atropine may have more serious adverse effects than the adhesive patch. Instead of irritating the skin and generating heat/sweat, as sometimes seen in patching treatments, atropine can induce vision-related side effects, including light sensitivity, conjunctival irritation, eye pain, and degraded pursuit tracking performance (11). Atropine can also induce systemic side effects such as headaches and tachycardia (12). These side effects can be more serious in specific patient populations, such as children with Down syndrome (13).

The literature consistently shows that compliance is overestimated when subjective measures such as self-reports are used (14,15). Although dynamic retinoscopy (16) and pupil fixation (17) were previously used to objectively estimate compliance to atropine penalization, these methods did not monitor the whole process and may have underestimated or overestimated objective compliance. So far, objective measurement of compliance to atropine penalization over time has not been reported.

Using medication event monitoring system (MEMS) devices, this pilot study aims to investigate objectively measured compliance (called "objective compliance" hereafter) to atropine penalization amblyopia treatment and to compare it to subjectively measured, or self-reported compliance (called "subjective compliance" hereafter).

Methods

The Institutional Review Board of Indiana University approved this research protocol and the study adhered to the tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act (HIPAA).

Study population

We enrolled children between the ages of 3 and 8 years with untreated, moderate, unilateral amblyopia, diagnosed and cared for by pediatric ophthalmologists at Indiana University School of Medicine. Informed consent was obtained from the subjects' parent or guardian (hereafter referred to as "parent"); assent was obtained from subjects 7 to 8 years of age.

Eligibility testing included the measurement of best-corrected visual acuity (VA) in both eyes using the standard ATS single-surround HOTV letter protocol (18) and a routine comprehensive eye exam (cycloplegic refraction, comprehensive ocular examination and a full motility examination).

Eligibility inclusion criteria: (I) ages range from 3 to 8 years old; (II) unilateral amblyopia: best corrected VA of the amblyopic eye ranging from 20/40 to 20/160. VA in the sound eye at least 20/40 or better. Interocular logMAR difference is at least two logMAR lines; (III) amblyopia associated with strabismus, anisometropia, or both; (IV) wearing of optimal spectacle correction (if needed) for a minimum of 12 weeks prior to enrollment. Details of the protocol for correction of refractive error followed guidelines from a previous PEDIG amblyopia treatment study of moderately amblyopic children (19); (V) previous patching treatment is allowed.

Exclusion criteria: (I) amblyopic eye has myopia (-0.25 D or more spherical equivalent); (II) known allergy to atropine eye drop; (III) previous atropine penalization amblyopia treatment; (IV) currently on other prescribed eye drops; (V) gestational age ≤ 32 weeks at birth; (VI) Down syndrome or developmental delays; (VII) previous intraocular surgeries.

Table 1 Baseline characteristics of the patients who had follow-up visits

Number of subjects	N=7
Gender (F/M)	2/5
Age (years), mean \pm SD (range)	5.2 \pm 1.5 (3.6 to 7.8)
Ethnicity (non-Hispanic/Hispanic)	6/1
Race (Caucasian/Black/Asian/other)	7/0/0/0
Cause of amblyopia (strabismus/anisometropia/combination)	3/2/2
Visual acuity in the amblyopic eye at baseline (logMAR), mean \pm SD (range)	0.52 \pm 0.07 (0.30 to 0.80)
Visual acuity in the fellow eye at baseline (logMAR), mean \pm SD (range)	0.07 \pm 0.09 (–0.10 to 0.20)
Severity of amblyopia, or interocular difference of visual acuity at baseline (logMAR), mean \pm SD (range)	0.45 \pm 0.23 (0.20 to 0.80)

Procedure

After confirming eligibility, a MEMS cap was assigned to each participant to assess objective compliance. MEMS caps are electronic devices that record the time and date when the bottle is opened. MEMS devices provide information about atropine application such as date and time and are a perfect fit for monitoring longitudinal compliance to atropine treatment. They have been successfully used to monitor compliance with pediatric glaucoma medication in older children (on average 10 years of age) for 3 months (20).

We used atropine sulfate 1% (5 mL, Falcon Pharmaceuticals, Fort Worth, TX, USA) for penalization, which is generally used in pediatric ophthalmology clinics. Participants were asked to store their atropine eyedropper in a bottle with the MEMS cap. The bottle-in-bottle approach has been used successfully in the past for glaucoma patients (20).

To assess subjective compliance, participants' parents were asked to mark a calendar log to indicate the days on which they instilled the eye drop.

Participants were scheduled for return visits at 4 and 12 weeks. Follow-up visits included a best-corrected VA measurement with ATS-HOTV, and both objective and subjective compliance recording.

Data and statistical analysis

The primary outcomes were compliance and improved VA after enrollment. Compliance was defined as the percentage of days in which atropine eye drop was taken compared to the number of doses prescribed. Objective compliance was calculated as the ratio of MEMS weekly recording times to weekly regimen. Weekly regimen was based on the

physicians' prescription, ranging from 2 to 7 drops per week.

In addition, actual dose in drops was counted as 1 drop for each recording of one opening; actual dose in grams was measured by weighing the eyedropper on a scale with a precision of 0.1 mg at every visit. Therefore, the weight change of the eyedropper during the treatment period can be calculated.

Due to the small sample size of this pilot study, descriptive statistics were mostly used. We fit the relationships between VA response and prescribed regimen, actual dose in drops and actual dose in grams, and used *t*-tests to assess the correlation coefficient of the fit.

Results

Ten children with amblyopia (20/40–20/125 in the amblyopic eye) were enrolled. A total of seven came back for 4-week follow-up, and six of them had 4-week VA measurements. The VA of one child was not measured because of atropine eye drop application in the morning of the visit. At the 12-week follow-up, six of the subject's visited back, and unfortunately only three of them brought the MEMS bottle back. Therefore, while we present an example of the 12-week follow-up, we focus on reporting data from the 4-week follow-up. The baseline characteristics of the patients are shown in *Table 1*.

Example of objective compliance with atropine penalization

Figure 1 shows both the objective and subjective compliance from an individual (IW) followed for 12 weeks. The overall average objective compliance for this patient (IW) was 57% while subjective compliance was 86%. As *Figure 1* clearly

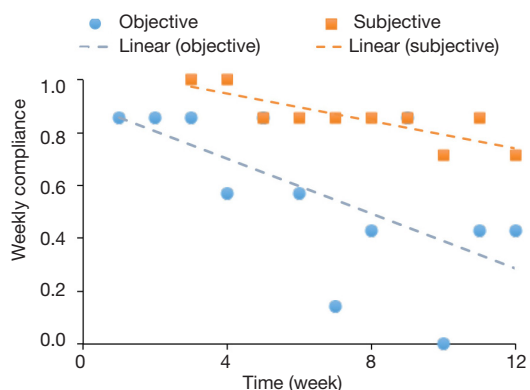


Figure 1 Both objective and subjective compliance over 12 weeks in a 6-year-old child with a daily regimen.

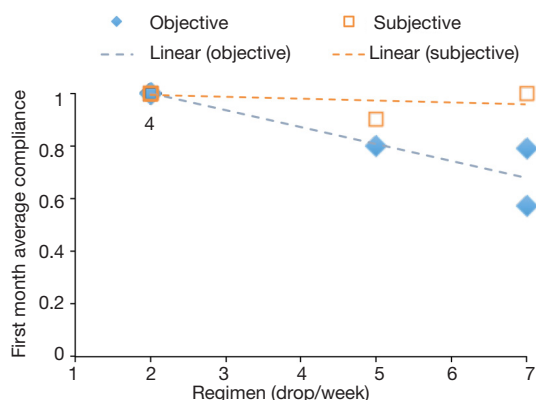


Figure 2 At the 4-week follow-up, both objective and subjective compliance are plotted according to regimen. The dashed lines show the trend. Note: (I) four patients with 2 drops per week regimen overlapped, so we marked “4” around the symbols; (II) one patient, with a 7-drop per week regimen, did not bring back the calendar log, the patient’s MEMS compliance was 0.57.

shows, subjective compliance is not enough to provide information about the detailed dosage over time. After the 8th week, the objective compliance of this patient was generally lower than 50%.

Summary of both objective and subjective compliance with atropine penalization

Figure 2 presents the average compliance over the first 4 weeks. It shows: (I) objective compliance decreases with regimen complexity; compliance is higher for 2-drop per week regimen compared to 7-drop per week regimen; (II) on average, subjective compliance is overestimated. At 4-week,

objective compliance averaged 88% (range, 57–100%), while subjective compliance was reported to be 98% (range, 90–100%); (III) interestingly, we found that the twice a week regimen showed a higher trend of objective compliance (100%) than the daily regimen (72%).

Prescribed regimen vs. response, actual dose in drops vs. response, and actual dose in grams vs. response

At the 4-week follow-up visit, VA improved 2.1 ± 1.7 lines ($n=6$, ranged from 0 to 4 lines). Figure 3A shows the prescribed regimen versus VA response relationship. The lower regimen patient (labeled CT, 2 drops/week) had a better response than a higher regimen patient (labeled IW, 7 drops/week). Figure 3B demonstrates the actual dose in drops versus response relationship. Figure 3C demonstrates the actual dose in grams versus response relationship. Note the data from patient CT (2 drops/week) and the data from patient IW (7 drops/week) correspond to different actual dose (in drop or in gram) and match the fitted line better in Figure 3C. Comparing these three fits, only the actual dose in grams versus response relationship is significant ($R^2=0.63$, thus $r=0.79$, two-sided t -test for correlation coefficient: $t=2.6$; $P=0.03$). The other two fits are not significant ($R^2=0.17$, thus $r=0.41$, two-sided t -test: $t=0.9$; $P=0.42$. $R^2=0.27$, thus $r=0.52$; two-sided t -test: $t=1.2$; $P=0.29$).

Discussion

This pilot study demonstrates that objective compliance with atropine penalization can be monitored with MEMS; objective compliance shows a trend for decreasing compliance over time and with increasing regimen frequency. Using the MEMS approach may facilitate more effective communication between clinicians and patients. Monitoring compliance objectively may provide further understanding of the patients’ parents’ compliance behavior and will lead to more precise and accurate dosage.

Although this was a pilot study with a small sample size, we have shown that objective compliance with atropine penalization is not always as high as expected or as patients’ parents report. It varies with individuals and is associated with regimen. This indicates that prescribing higher regimen may not be as effective as expected because patients may not comply as well with a regimen that requires more frequent drop instillation. In addition, instructions for instilling eye drops in patients’ eyes is often vaguely described on the commercial eyedropper; it says “instill 1–2

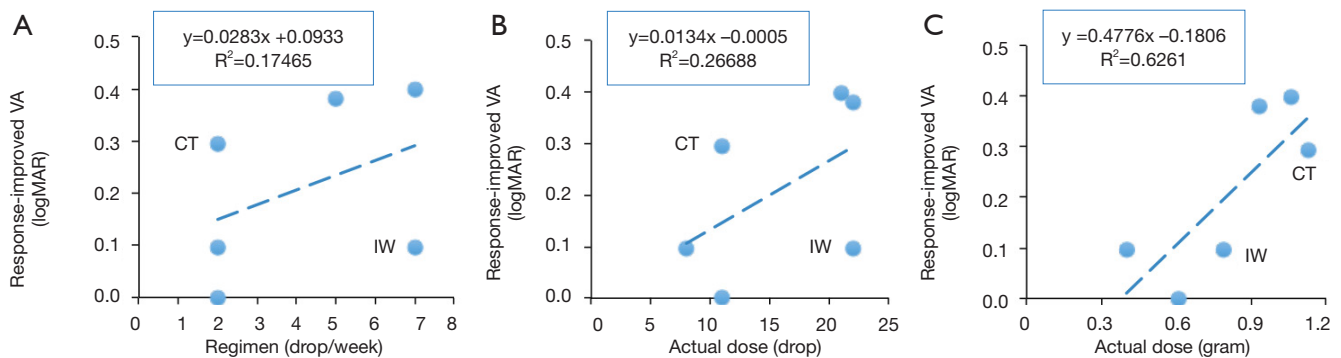


Figure 3 VA improvement response at 1-month follow-up for atropine penalization treatment (n=6). (A) Prescribed regimen versus response relationship; (B) actual dose in drops versus response relationship; (C) actual dose in grams versus response relationship. Note the data from patient CT (2 drops/week) and the data from patient IW (7 drops/week) correspond to a different actual dose (in drops or in grams) and match the fitted line more in (C).

drops". Thus, we may not know the actual dosage applied to patients.

As Figure 3C shows, although prescribed with a more frequent regimen, patient IW did not actually instill a higher dosage of eye drops compared to patient CT, who was prescribed with a less frequent regimen. Such findings suggest that we cannot merely count on prescribed regimen. Our pilot data showed that the actual dose in gram versus response relationship is a better fit. Although it is not robust to conclude with such a limited sample size, our approach demonstrated the potential to probe the actual dose in grams versus response relationship with more information from quantitative measurement.

In addition to the small sample size, this study is limited by a few assumptions: (I) we assumed that one opening of the bottle corresponded to one instillation of eye drop; (II) we assumed that a decreasing eye drop bottle weight corresponds to the volume of atropine instilled into the eye. Even given these assumptions, the objective estimate of compliance and amount of eye drops still provides more quantitative information than previous studies.

Atropine penalization was recommended as a first-line treatment for amblyopia, but it has not been widely applied in clinical settings (21,22). One reason could be that there is no study to clarify the dose-response relationship in atropine penalization treatment. The findings from a previous study indicate that a daily regimen (7 drops/week) of atropine penalization is equally effective as a weekend regimen (2 drops/week) for both moderate and severe amblyopia (23). However, the similar outcomes between the daily and weekend cohorts may have resulted

from differences in patient compliance. Without objective compliance measurement, it is impossible to know whether the daily regimen group instilled the drops on a daily basis. To date, no clear evidence exists regarding the dose-response relationship between atropine treatment and visual outcome. Thus, our pilot study points to the importance of defining a clear dose-response relationship and assessing objective compliance to atropine penalization.

An investigation of compliance and further dose-response of atropine treatment is critical for the following three reasons: (I) as a pharmaceutical, atropine may have more serious side effects than the adhesive patch. Thus, it is critically important to find the minimal atropine dose needed to achieve effective vision improvement; (II) unlike patching, which can be immediately removed, atropine affects accommodation, pupil size, and near VA for more than 72 hours (24). As has been previously reported, atropine treatment has a risk of inducing reverse amblyopia (degraded vision in the treated eye) if not monitored closely (25,26). Thus, the question of when to cease atropine treatment is pivotal; (III) atropine may take a longer time to be effective than patching. In a randomized clinical trial conducted by PEDIG on patching and atropine, after 5 weeks 56% of patients were successfully treated in the patching group and only 33% in the atropine group; by 6 months, these percentages were similar (79% and 74%, respectively) (3,7). This finding indicates that atropine treatment requires compliance for a longer period. At this point, we have very little information about the dose-response relationship and more experiments with longer follow-up should be designed to explore these questions.

Conclusions

Objective compliance with atropine penalization instructions can be monitored with a MEMS bottle; objective compliance shows a trend for decreasing compliance over time and varies with regimen and individuals. On average, subjective parental reporting of compliance has an overestimated trend.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The Institutional Review Board of Indiana University approved this research protocol (No. 1310504045) and the study adhered to tenets of the Declaration of Helsinki and to the Health Insurance Portability and Accountability Act (HIPAA), and written informed consent was obtained from all patients.

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