Side Effects of Atropine (SEA) Study

NCT03593044

November 23, 2021

Research Protocol
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Version 1.0

I. Objectives

The purpose of this study is to determine whether there are any changes in subjective or objective measures of eye comfort or vision. Specifically, we will monitor for the following changes:

1. High contrast distance, high contrast near, and low contrast distance visual acuity
2. Pupil size
3. Ability to focus the eyes for near work
4. Reading speed
5. Subjective comfort and vision issues
6. Headaches
7. Intraocular pressure

We hypothesize that pupil size will increase significantly, but no other measures will change clinically meaningfully.

II. Background and Rationale

1.0% atropine is routinely used to dilate pupils and knock out the ability to focus the eyes to see close objects clearly, and it also slows the progression of nearsightedness. Many eye care practitioners are now using 0.01% atropine to slow the progression of nearsightedness because it slows the progression of nearsightedness by 60%[1] to 83%,[2] and it causes much fewer side effects than 1.0% atropine. One study compared myopia progression and side effects of 0.01%, 0.1%, and 0.5% atropine in children. While 0.5% atropine slowed myopia progression significantly more than 0.01% atropine, there were no other differences in myopia progression over two years, and there were fewer side effects with 0.01% atropine (Table 1), so many eye care practitioners now use 0.01% atropine to slow the progression of nearsightedness.

Table 1. Ocular changes after taking various concentrations of atropine.

	0.01%	**0.1%**	**0.5%**	**p-value**
Accommodative amplitude (D)	-4.6	-10.1	-11.8	<0.001
Pupil size in dim light(mm)	1.15	2.71	3.56	<0.001
Pupil size in bright light (mm)	0.75	2.24	3.11	<0.001
Distance visual acuity (logMAR)	-0.02	+0.01	-0.01	0.44
Near visual acuity (logMAR)	-0.02	+0.06	+0.25	<0.001
Asked for glasses to improve near vision (% yes)	6	61	70	<0.001

Another study examined the changes in visual function and symptoms of young adults while taking daily drops of 0.01% atropine for five days. Only pupil size and pupil response exhibited a significant change over that time period (Table 2).

Table 2. The change in vision function while taking 0.01% atropine for five days.

	Day 1	**Day 3**	**Day 5**	**p-value**
Distance VA (logMAR, OD)	-0.10 ± 0.10	-0.08 ± 0.07	-0.08 ± 0.05	0.55
Near point of accommodation (D)	10.2 ± 1.42	10.0 ± 1.39	9.1 ± 2.12	0.08
Pupil size (mm, OD)	5.51 ± 1.74	6.55 ± 1.12	6.82 ± 0.61	0.04
Pupil response	3.0 ± 0.0	2.8 ± 0.5	1.1 ± 0.9	<0.01
Reading speed (words per second)	3.36 ± 0.55	3.16 ± 0.54	3.25 ± 0.45	0.12
Near point of convergence (cm)	6.8 ± 2.4	7.0 ± 2.2	8.0 ± 3.2	0.25

We plan to examine a wider range of objective measures of visual function and symptoms than previous investigations, including investigate the changes in vision, pupil size, the ability to focus the eyes for near work, reading speed, comfort of the drops, subjective visual effects, presence and severity of headaches, and whether or not someone would be willing to take the drops long-term if they delayed the onset of nearsightedness.

III. Procedures

A. Research Design

This is a prospective cohort study in which we will compare pre-treatment measures to post-treatment measures after taking the treatment for approximately one week. The subjects will serve as their own controls. This will allow us to see the changes to be expected while taking the eye drop. Because the half-life of the drug is approximately 4 hours and maximum cycloplegia (eyes can't focus for near work) occurs in less than one hour, a longer period of time is not required.

B. Sample

We will examine adults between the ages of 21 and 30 years. We are not examining the effects in children because adults will give a more accurate description of the side effects they experience than children. Because children typically complain less about eye comfort and vision issues than adults,[3] we strongly believe that we will obtain data that would be considered the worst case scenario for children. The specific entry criteria are listed in Table 3.

Table 3. Entry criteria

Age	21 to 30 years, inclusive
Accommodation	No known history of accommodative issues or therapy

All subjects in the age range specified with no known accommodative (focusing) issues will undergo consent and be enrolled.

Most of this experiment is hypothesis generating, but we can estimate a sample size based on a two measures, assuming $\alpha = 0.05$ and power = 80%. We aim to detect a change in pupil size of 1.0 mm because this is approximately what was reported in previous studies and what may begin to be clinically meaningful. We conservatively estimate a SD of change of 1.0. We also aim to detect a change in visual acuity of 0.1 logMAR, which is one line of visual acuity, a clinically meaningful change, with a standard deviation change of 0.2. The sample size required for pupil size is eight subjects and the sample size for visual acuity is 31 subjects. We will aim to enroll a sample sufficient to detect both the pupil size and visual acuity change. Assuming a 10% drop out rate, we estimate a sample size of 35, and we include five extra subjects who may be ineligible, for a total sample size of 40 subjects.

C. Measurement / Instrumentation

Manifest Refraction

This is a standard clinical procedure used to measure glasses prescriptions during clinical examinations. Cycloplegic autorefraction, the standard measure of eye prescription in many studies, is not necessary because we are not measuring the change in prescription over time.

Phoria

We will measure phoria at near in order to determine whether low concentration atropine affects how the two eyes work together Modified Thorington is a more repeatable and less subjective method of measuring phoria than alternating cover test.

Visual Acuity

We will measure the high contrast (black letters) visual acuity at distance and near and the low contrast (grey letters) at distance using logMAR visual acuity charts and scoring on a letter basis. These measures of vision are standard protocols for vision research.

Pupil Size
We will measure the pupil size with the NeurOptics VIP-200 Pupillometer (NeurOptics, Inc., Irvine, CA) in bright and dim light. For the dim light condition, the subject will stand with his or her back toward the wall-mounted visual acuity chart with the room lights off except for the incandescent lamp pointed straight down over the examination chair at the opposite end of the room. For the bright condition, the subject will stand with his or her back toward the wall-mounted visual acuity chart, and the visual acuity chart illumination should be turned on and be the same as when taking visual acuity measurements (approximately 75 – 120 cd/m^2 or 9.3-9.9 EV).

Focusing Ability
A detailed target on a stick will be too near the eyes to read the letter. The stick will be pulled away from the subject until the subject reads the letter. The distance between the forehead and the stick will be measured to determine the ability to focus.

Lag of Focus
While wearing full vision correction, the prescription will be measured ten times while looking at distance target using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL). A target will then be placed at 33 cm, and the subject will be told to keep the target clear while measuring the prescription five times. The prescription at distance will be subtracted from the prescription at near, and that result will be subtracted from 3.0 D, which is the focusing demand.

Reading Speed
Reading Speed will be measured using the Rate of Reading Test. This test contains the same 15 simple words, repeated on each line and presented in random order. It is meant to serve as a test of reading speed pre- and post-intervention.

Ability to Shift Focus
Subjects will view a card held at 40 cm. Flippers with +2.50 D lenses on one side and –2.50 D lenses on the other side will be placed in front of the subject, and the subject will report when the letters become clear. The lenses will be flipped, and the subject will again report when the print is clear. This will be continued for 1 minute, and the number of flips will be counted. This is a routine clinical measure of the ability to change focus from distance to near.

Surveys
We will survey subjects about light sensitivity, drop comfort, likelihood of taking the drop to delay the onset of nearsightedness, vision symptoms, headaches, and comfort of the proparacaine eye drop and an artificial tear eye drop (for comparison of drop comfort to low concentration atropine). We will use the following format to collect survey data (using different questions and anchors as necessary):

Overall, what did you think of your vision during the past three days?

1	2	3	4	5	6	7	8	9	10
Good									Perfect

Pressure in the Eye
We will measure the pressure in the eye using a Tonopen, a clinical measure that is performed during routine eye examinations. This requires a drop of 1% proparacaine in each eye to numb the eye. This drop is also used during routine eye examinations.

D. Detailed Study Procedures
Manifest Refraction
The examiner will measure glasses or perform retinoscopy to get a starting point for the refraction. The refraction will be performed using Jackson crossed cylinder, binocular blur balance, and maximum-plus-to-maximum-acuity to obtain the final refraction.

Phoria

The subject holds the Maddox rod horizontally in front of the right eye for 30 seconds before testing. Hold the near Muscle Imbalance Measure (MIM) card 40cm from the subject. Encourage the subject to keep the letters and numbers on the card clear, and shine the penlight through the hole in the center of the card. Ask the subject whether the red line is on the side of the red triangle (esophoria) or the blue circle (exophoria), and have the subject to tell you the number the line goes through. The card is marked with even numbers only, so if the subject states that the line is between two numbers, record the number between them (for example, if the line is between the 2 and the 4 on the red triangle side of the card, record 3pd esophoria). Record the finding using a positive sign (+) to indicate **eso** deviations and a negative sign (–) to indicate **exo** deviations.

Visual Acuity

Bailey-Lovie logMAR charts will be calibrated to 9.3 to 9.9 EV (75 to 120 cd/m^2). The subject stands 4 meters from the chart and reads the first letter on each line, continuing down the chart until the first letter is missed. She starts two lines above the missed letter and reads five letters from every line. If she misses a letter on the first line, she continues up the chart until she reads all five letters correctly. She must guess five letters on each line until three or more letters is missed in a single line. If she gets 3 or more correct on the bottom line, move to 6 meters and repeat. If she does not get all five letters correct on the top line, move the subject to 2 meters and repeat. The total number of letters read correctly and the final test distance are recorded for each visual acuity measurement.

Pupil Size

Press the OD button to activate the unit. Bring the unit up in front of the subject's right eye with the eye cup resting against the subject's face and hold down the OD button continuously. When the pupil is marked with a green circle, release the button to initiate the measurement. Hold the unit still during the few seconds of the measurement. Take care that the eyelids do not cover the pupil. If the green measurement circle was not centered over the pupil, delete the measurement by using the Eraser icon at the right side of the three-icon Tool menu. Repeat the measurement until the green measurement circle is centered over the pupil. Record the pupil size to the nearest 0.1 millimeter on the examination form. Repeat steps 6-9 while the lights are in the mesopic condition.

Focusing Ability

A letter target on a stick is placed against the nose, in front of the eyes. Tell the subject the stick will be moved slowly away until the subject can first read the letter correctly. The subject should say the letter as soon as s/he can read it. The distance from the forehead to the stick is measured to the nearest cm and recorded.

Lag of Focus

Place the manifest correction used for visual acuity in a trial frame, minimizing the number of lenses used in the trial frame. Place an occluding trial lens in the trial frame well over the left eye so that the subject will only view targets with the right eye. Place the 33cm near rod in the central slot to measure accommodative lag in primary gaze only. Place the subject's chin on the chinrest and forehead against the forehead rest. Obtain a view of the eye on the screen. The white keratometry circle should be in focus. Centered the pink reticule within the white keratometry ring. Encourage the subject to keep the letters as clear as possible throughout the measurement and have the subject focus on a specific letter to ensure the subject is attentive and accommodating. Obtain at least five readings without the "retry" message. When in doubt, take additional measurements to ensure that at least 5 measurements exist. Press Print and tape the printout in the location indicated on the exam form.

Reading Speed

Tell the subject you want him/her to read the random words on a page as quickly as possible without making any mistakes. If you make a mistake, just continue reading the card. You will read for one minute. I will tell you when to start and when to stop. Have the subject hold Test A at 40 cm. Tell the subject to being and immediately begin the stop watch. Put a line through each mistake. Circle the last word read correctly and record the number of words read correctly. If more than five mistakes occurred, have the subject read for another minute and continue until the subject makes five or fewer mistakes.

Ability to Shift Focus
Subjects hold the near visual acuity card at 40 cm. Flippers with +2.00 D lenses on one side and –2.00 D lenses on the other side will be placed above the subject's eyes. Tell the subject to say "now" as soon as the letters on the card are clear after each flip of the lenses. This will be timed for one minute, and the number of cycles will be recorded. Begin with the +2.00 D lenses and measure binocularly.

Surveys
Subjects will be told to circle the number that corresponds to their perception that answers each question, noting the descriptions at each end of the numbers.

Pressure in the Eye
Place one drop of 1.0% proparacaine in each eye of the subject, and have him/her answer the three questions about eye comfort after receiving the drop. Place a sheath on the measurement tip of the Tonopen. Have the subject view a distant object while holding the eye open. Press the button on the Tonopen and wait until the green light turns on. Lightly tap the Tonopen on the cornea, until a final "beep" sounds. If the screen has a "95" in the bottom right corner, then the measure is valid and can be recorded. If anything else is displayed, repeat the procedure.

Compounding of the 0.01% Atropine
The drug will be compounded by the Central Ohio Compounding Pharmacy. They will dissolve 0.1 g atropine sulfate USP monohydrate powder in 1000 mL sterile water to a final concentration of 0.01%, and add Benzalkonium Chloride as preservative.

E. Internal Validity
We will measure the potential side effects of low concentration atropine in adults rather than children, although children will ultimately receive low concentration atropine for myopia control. We are not examining the effects in children because adults will give a more accurate description of the side effects they experience than children. Because children typically complain less about eye comfort and vision issues than adults,[3] we strongly believe that we will obtain data that would be considered the worst case scenario for children.

We will use a pre- post-test format in order to examine the changes to be expected over a short period of time. The first week of experience will typically guide the likelihood of long-term commitment to the treatment.[4,5] We therefore want to know how much administration of low concentration atropine will have on subjects' vision.

F. Data Analysis
We will perform repeated measures t-tests to determine whether there are significant changes over time for normally distributed variables and Wilcoxon signed-rank tests to determine whether there are significant changes over time for non-normally distributed variables.

IV. Bibliography

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