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Bifocal & Atropine in Myopia (BAM) Study: Baseline Data and Methods

Juan Huang, PhD, OD, FAAO, Donald O. Mutti, OD, PhD, FAAO, Lisa A. Jones-Jordan, PhD, FAAO, and Jeffrey J. Walline, OD, PhD, FAAO

The Ohio State University, College of Optometry, Columbus, Ohio

Abstract

Significance.—The Bifocal & Atropine in Myopia (BAM) Study aims to determine whether combining 0.01% atropine and +2.50-D add center-distance soft bifocal contact lenses (SBCL) slows myopia progression more than SBCL alone. The results could provide significant information on the myopia control effect of combining optical and pharmacological treatments.

Purpose.—This article describes the subject characteristics at baseline, the study methods, and the short-term effects of this combination treatment on visual acuity (VA) and vision-related outcomes.

Methods.—BAM subjects who met the baseline eligibility criteria were dispensed the combination treatment for two weeks to determine final eligibility. Outcome measures included VA at near and distance (Bailey-Lovie logMAR charts), near phoria (Modified Thorington), accommodative lag (Grand Seiko WAM-5500), and pupil size (Neuroptics VIP-200 Pupillometer). Compliance was monitored using surveys. Two subgroups in the Bifocal Lenses In Nearsighted Kids (BLINK) Study, single-vision contact lens wearers and those who wore +2.50-D add SBCL, will serve as the age-matched historical controls for BAM Study.

Results.—Forty-nine BAM subjects (9.6 ± 1.4 years) were enrolled; mean spherical equivalent cycloplegic autorefractive was -2.33 ± 1.03 D. After two weeks of treatment, the best-corrected low-contrast (10% Michelson) distance VA was reduced (pre-treatment = $+0.09 \pm 0.07$, post-treatment = $+0.16 \pm 0.08$; $P < .0001$), but the high-contrast VA at near or distance was unaffected. Near phoria increased by about 2 in the exo direction ($P = .01$), but the accommodative lag was unchanged. The pupil size was not significantly different between pre- and post-treatment for either the photopic or mesopic condition. Surveys indicated the subjects wore SBCL $77 \pm 22\%$ of waking hours and used atropine 6.4 ± 0.7 days per week.

Conclusions.—Two weeks of combination treatment reduced low-contrast distance VA and increased near exophoria slightly, but the subjects were compliant and tolerated the treatment well.

Keywords

soft bifocal contact lenses; atropine; myopia

The current mainstream strategies for myopia control include pharmacological agents (atropine) and optical treatments, such as orthokeratology and soft bifocal/multifocal contact lenses.^{1–9} Among the investigated interventions, atropine provides the most effective myopia control, while orthokeratology and soft bifocal/multifocal contact lenses had moderate effects.^{5–7, 9} Center-distance soft bifocal contact lenses slowed myopia progression by between 25 and 72%,^{9–17} and orthokeratology reduced axial elongation by about 35 to 55%,^{9, 18–21} both with few side effects. The presumed mechanism for the myopia control effect of soft bifocal contact lenses and orthokeratology could be due to the myopic defocus that extends into the periphery, a robust inhibiting signal for slowing ocular growth.^{22–28}

Clinical studies show that atropine slows myopia progression in a dose-dependent manner, with higher concentration being more effective.^{4, 29, 30} However, fewer side effects (such as pupil dilation and the reduction in accommodation) with 0.01% atropine make it an appealing myopia control option. Low concentration 0.01% atropine slowed myopia progression by 30% - 60% while significantly mitigating potential side effects.^{29, 30} Compared to higher concentrations, 0.01% atropine exhibited less increase of refractive error progression after atropine cessation.³¹ The mechanism of slowing myopia progression with atropine remains controversial.^{32–34}

Combining pharmacological and optical treatments could provide additive myopia control. Options for the combination treatment include different concentrations of atropine and various optical corrections. In a clinical trial that combined multifocal spectacles with 0.5% atropine,³⁵ the combination treatment slowed the progression of myopia significantly more than each treatment alone. Two other recent studies also found that combining atropine and orthokeratology contact lenses was more effective in slowing axial elongation than orthokeratology alone.^{36, 37} These studies indicate that combination treatments may provide better myopia control than one treatment alone, supporting the justification for evaluating the effect of combining 0.01% atropine and soft bifocal contact lenses.

It is possible that the choroid is involved in the mechanism of the additive myopia control effect by combining pharmacological and optical treatments. Studies in humans and animals show that the choroid thickens and thins in response to short-term optically induced myopic and hyperopic defocus, respectively, and the changes in choroidal thickness correlate with changes in axial elongation.^{38–40} Additionally, intravitreal injection of atropine in chicks results in rapid, transient choroidal thickening and slowed axial elongation.⁴¹ In humans, administration of atropine eye drops increased choroidal thickness and inhibited choroidal thinning induced by hyperopic defocus.^{42, 43} Since both atropine and optical defocus affect myopia progression, and both can cause changes in choroidal thickness, it is reasonable to speculate that the pharmacological and optical myopia control mechanisms might share a pathway that involves the choroid.

The Bifocal & Atropine in Myopia (BAM) study investigates whether combining the pharmacological effect of 0.01% atropine and the optical effect of soft bifocal contact lenses results in greater slowing of myopia progression than soft bifocal contact lenses alone. Addressing this research question is significant because the results may lead to novel strategies that optimize the effect of myopia control through combined pharmacological and

optical interventions. In addition, this study will be the first to assess the relationship between early short-term changes in choroidal thickness and long-term myopia progression in children. If they are correlated, then short-term changes in choroidal thickness might be useful for predicting the long-term outcome of anti-myopia treatment.

This article describes the baseline characteristics of the subjects enrolled in the BAM Study, the study methods, and the short-term effects of the combination treatment on visual acuity and vision-related outcomes.

METHODS

The BAM Study is an ancillary study of an ongoing National Eye Institute-funded randomized clinical trial, the Bifocal Lenses In Nearsighted Kids (BLINK) study, which compares the myopia progression rate between subjects wearing single vision soft contact lenses and those wearing soft bifocal contact lenses.⁴⁴ Between October 17, 2014 and June 20, 2016, the BLINK Study enrolled 294 myopic children aged 7 to 11 years at two clinical centers: The Ohio State University (OSU) College of Optometry and The University of Houston College of Optometry (UHCO). The subjects in the BLINK Study were randomly assigned to wear either single vision soft contact lenses or soft bifocal contact lenses with either a +1.50-D add or +2.50-D add power for three years to test the hypothesis that soft bifocal contact lenses slow myopia progression in a dose-dependent manner in children.⁴⁴ Forty nine subjects who wore soft bifocal contact lenses with +2.50-D add power and another 49 single-vision contact lens wearers from the BLINK Study will serve as the age-matched historical control groups for the 49 subjects enrolled in the BAM Study. The subjects in the BAM Study will wear soft bifocal contact lenses in combination with daily administration of 0.01% atropine for three years, and the rates of myopia progression and axial elongation will be compared to those in the corresponding groups in the BLINK Study. In addition, the BAM Study will evaluate the relationship between short-term changes in choroidal thickness and long-term effects on myopia progression and axial elongation. The subject eligibility criteria and protocol for the outcome measures in the BAM Study are consistent with the BLINK Study.

Study Aims

The BAM Study will investigate two specific aims:

Specific Aim 1: To test whether the combined treatment of 0.01% atropine and soft bifocal contact lens wear produces slower myopia progression and axial elongation compared to soft bifocal contact lenses alone over 3 years.

The three-year change in spherical equivalent refractive error and axial length of subjects undergoing the combined treatment in the BAM Study will be compared to age-matched subjects wearing only soft bifocal contact lenses in the BLINK Study.

Specific Aim 2: To test whether early changes in choroidal thickness can be used as predictors of long-term myopia progression / axial elongation.

The change of choroidal thickness from before treatment until two weeks after starting treatment will be measured in the subjects receiving combination treatment in the BAM Study and those using soft bifocal contact lenses alone in the BLINK Study. The correlation between the 2-week change in choroidal thickness and 3-year rate of myopia progression / axial elongation will then be investigated in each group.

Human Subjects Protection

The study protocols were approved by The Ohio State University Biomedical Institutional Review Board, and the research was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). After providing informed consent, parental permission was obtained from a parent or guardian, and assent was obtained from the subject. Parental permission from parents of the OSU BLINK Study subjects was also obtained prior to using the data collected for the BLINK Study. The study is registered with clinicaltrials.gov (NCT03312257).

Subjects

The subject eligibility criteria at baseline were consistent with the BLINK Study, and the rationale for the parameters have been described in detail.⁴⁴ Briefly, the age range was 7 to 11 years, inclusive. In each eye, the amount of myopia allowed was -0.75 to -5.00 diopter (D), spherical component (minus cylinder convention), and no more than 1.00 D of astigmatism. The amount of anisometropia was limited to no more than 2.00 D difference in the spherical component between the eyes. All refractive error entry criteria were based on cycloplegic autorefraction. The best-corrected visual acuity at distance had to be $+0.1$ logMAR (20/25) or better in each eye with spectacle correction and $+0.1$ logMAR (20/25) or better binocularly while wearing $+2.50$ -D add soft bifocal contact lenses. Previous gas-permeable, soft bifocal, or orthokeratology contact lens wear was limited to no more than 1 month by subject or parent report, and previous participation in myopia control was also limited to 1 month. No subject had any previous experience with myopia control treatment prior to enrolling in the BAM Study. Subjects also needed to be in good general and ocular health, and could not be chronically using medications that may affect immunity, such as oral or ophthalmic corticosteroids. In addition, subjects needed to pass the run-in period to be enrolled in the study (see more details in the “run-in period” section below).

Subjects who met the eligibility criteria at the baseline visit were dispensed $+2.50$ -D add soft bifocal contact lenses and 0.01% atropine at the 1-week visit. The children were asked to wear contact lenses during waking hours as often as they could comfortably do so and use one drop of 0.01% atropine in each eye every night before bed, after removing contact lenses. The children then returned to the clinic for the 3-week visit to determine their final eligibility. Subjects enrolled in the BAM Study will be age-matched to subjects who wear single vision soft contact lenses and those who wear soft bifocal contact lenses with $+2.50$ -D add power in the BLINK Study.

Run-in Period

The timeline of the run-in period was between 1-week and 3-week visit, and the purpose of the run-in period was to ensure adequate compliance with atropine use. In order to pass the

run-in period, subjects needed to use 0.01% atropine eye drops, on average, at least 5 days each week (about 71%) based on self-reported calendars and a decrease in bottle weight consistent with that amount of usage. A calendar was given to the subject at the 1-week visit, and he/she was required to circle “yes” or “no” every day to answer the question “*Did you use the eye drops today?*” The subject was asked to bring the completed calendar to the clinic at the 3-week visit. Parents also completed surveys on atropine compliance and side effects at the 3-week visit. In addition, investigators weighed the atropine bottle at the 1-week visit before giving it to the subject, and then weighed the atropine bottle again at the 3-week visit. The difference in bottle weight between the 1-week and 3-week visit was the nominal weight of atropine usage during the run-in period. The subjects were considered to be compliant with atropine treatment if the decrease in bottle weight indicated using atropine for at least 5 days per week (about 71%), calculated by dividing the nominal weight by expected weight of atropine usage during the run-in period (estimated weight of one drop of atropine 0.0368 g X total days during the run-in period X 2). Investigators emphasized the importance of daily use of atropine, but the subjects and parents were not told that they needed to use the atropine eye drops at least 5 days per week or that the bottle would be weighed to avoid potential bias.

Visits

Table 1 lists the schedule of measurements for the BAM Study. Subject’s eligibility was assessed at the baseline visit, and all the subsequent visit dates were calculated based on completion date of the baseline visit. At the 1-week visit, subjects were taught contact lens insertion, removal, and care, and the subjects and their parents were given instructions on how to use atropine eye drops. Contact lenses and atropine were dispensed at the one week visit. At the 3-week visit, subject’s final eligibility was determined based on the atropine use during the run-in period. During the semi-annual (6-, 18-, and 30-month) visits, the ocular health and contact lens fit were evaluated, and surveys related to contact lens and atropine use were administered. During the annual (12-, 24-, and 36-month) visits, all outcome measurements were performed, the ocular health and contact lens fit are evaluated, and surveys related to contact lens and atropine use were administered.

Adverse Events

Adverse events were closely monitored throughout the study. At each visit, adverse events were solicited by asking parents the question “*Has your child experienced any changes in his or her eyes, vision, or health since the last visit?*” The examiner also asked the subject and parent about specific symptoms from a checklist, which included symptoms of burning or stinging, itching, dryness, poor comfort at the end of the day, excessive tearing or discharge, blurry vision, sensitivity to light, and headache. Additionally, the parent completed a survey regarding ocular and systemic side effects of atropine, including light sensitivity, blurred vision at distance and near, dry mouth, fever, and mental confusion. The severity of these symptoms was categorized as “mild”, “moderate”, and “severe”; the frequency of the symptoms was categorized as “*infrequently (not very often)*”, “*sometimes*”, “*fairly often*”, and “*always*”. If the examiner determined the condition was significant and led to daily activity change over an extended period or if the condition required medical attention (such as a broken arm), then the condition was determined to be an adverse event. Presentation of

ocular signs or symptoms worse than those encountered during routine eye care and contact lens wear, such as slit lamp signs greater than grade 3, were also deemed to be adverse events. All adverse events, regardless of whether they were determined to be related to the treatment of contact lens and/or atropine, were documented. All adverse events were categorized as ocular/non-ocular, serious/non-serious, mild/moderate/severe, contact lens wear discontinued/temporarily discontinued/permanently discontinued, and expected/unexpected.

Sample Size

Estimates of sample size were computed for each specific aim using PASS 2005 software using $\alpha = 0.05$ and $\beta = 0.20$ (power =80%) and then combined to determine the optimal sample size to address both aims.

The primary analysis will compare the myopia progression between the group that received combination treatment and the age-matched group that received +2.50-D add soft bifocal contact lens treatment alone. Axial length elongation will also be compared between the two groups, although the primary outcome is change in refractive error and was used for sample size calculation. Myopia progression will be evaluated using the mean value of ten cycloplegic autorefraction spherical equivalent readings. To compare results at year three while using all available data, a repeated measures analysis of covariance (ANCOVA) will be performed. Walline and colleagues showed that the mean ($\pm$ SD) myopia progression of single vision soft contact lens wearers was $-1.29 \text{ D} \pm 0.71$ over three years.⁴⁵ The proposed myopia progression in the +2.50-D add soft bifocal group for the sample size calculation of the BLINK Study based on a 50% treatment effect was -0.65 D . The addition of atropine to the +2.50 D add bifocal lenses is expected to reduce progression by a further 50% for a total progression of 0.33 D over three years. Using a standard deviation of 0.71 D and taking into account the pair-matched design, the sample size for this aim is 39 subjects per group at $\alpha = 0.05$ and a study power of 0.20.

The secondary analysis will determine whether early changes in choroidal thickness could be used as a predictor of long-term change in myopia progression and axial elongation. Pearson correlations and linear regression models will be used to examine the relationship between the amount of short-term changes in choroidal thickness (2-week period between 1-week visit and 3-week visit) and the resulting myopia progression/axial elongation. Regression models will include the change in choroidal thickness as well as any necessary covariates. The correlation between choroidal thickness and refractive error/axial length ranges from 0.35 to 0.74 based on previous studies,^{46–48} although none of these studies evaluated short-term change in choroidal and long-term progression of refractive error. A sample size of 44 per group will allow for detecting a correlation of 0.41 between short-term changes in choroidal thickness and long-term myopia progression/axial elongation.

Using the maximum required sample size (39 subjects for aim 1, and 44 for aim 2) and adjusting for 10% loss to follow-up (based on an conservative estimate from the BLINK Study)⁴⁴ gives a total sample required of 49.

Contact Lens Options

All subjects wore Biofinity Multifocal “D” with a +2.50-D add power contact lenses, the same primary contact lenses used in the comparison group in the BLINK Study.⁴⁴ If a subject exhibited a poor fit (limbal exposure, excessive movement, or no movement) during follow-up, Proclear Multifocal “D” contact lenses were used as the alternative contact lens due to its similar optical profile to Biofinity Multifocal “D” contact lenses.⁴⁴ Table 2 lists the basic parameters of the Biofinity and Proclear Multifocal “D” contact lenses. Contact lenses, solutions, and contact lens cases were provided free of charge for all subjects. The initial contact lens power was determined by the spherical equivalent power (after referencing to the corneal plane) of the manifest refraction performed by a licensed study optometrist.⁴⁹ Over-refraction of the contact lens power was performed at each study visit and the contact lens prescription was updated if the over-refraction was greater than −0.50 D, or if the change was deemed to be clinically necessary. Study subjects were told to wear their contact lenses as often as they would like during waking hours (no overnight wear), and a pair of free or reduced-cost spectacles was also provided for the subjects. At each visit after the subject was enrolled in the study, the subject and parent completed surveys regarding their contact lens wear time during each week. Specifically, they were asked how many days they usually wore contact lenses and what time they usually inserted and removed contact lenses during weekdays and weekends, respectively. Parents were also asked what time the children typically woke up and went to sleep. Percentage of contact lens wear time during waking hours per week was then calculated based on the information. Additionally, the subjects were asked to rate their vision, comfort, and satisfaction with their contact lens wear.

0.01% Atropine Ophthalmic Solution

The atropine ophthalmic solution was compounded by dissolving atropine sulfate USP (United States Pharmacopeia) monohydrate powder in sterile water to a final concentration of 0.01% (for every 0.1 g of atropine, 1000 ml of sterile water was added), and Benzalkonium Chloride was added as preservative. The compounding was performed in a sterile manner according to the USP guidelines at a local compounding pharmacy located in Columbus, OH. The 0.01% atropine ophthalmic solution was provided to the subjects free of charge, and used within 120 days from the date of compounding.

Parents completed surveys on atropine compliance at each visit after the subject started using atropine. The compliance survey asked how many days during the week (0 to 5) and weekend (0 to 2) the children typically missed the atropine drops, and the reason(s) the subjects missed the eye drops. Both oral and written detailed instructions on how to apply atropine were given to the parents. The subjects and parents were educated on the side effects of atropine, and instructed to contact the study personnel immediately if they experienced a red eye, eye pain, or any vision- or life-threatening events related to the use of prescribed atropine.

Outcome Measurements

The protocol for the outcome measures in the BAM Study is consistent with the BLINK Study. This article summarizes the outcome measurements that have been previously described in the BLINK Study⁴⁴, and provides more detailed information on the

measurements of choroidal thickness, which was not described in the baseline paper of the BLINK Study.

Central Refractive Error

The 3-year change in spherical equivalent refractive error determined by cycloplegic autorefraction using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL) is the primary outcome of the BAM Study. To achieve cycloplegia, one drop of 0.5% proparacaine was instilled and followed by two drops of 1.0% tropicamide, five minutes apart. Cycloplegic measures were performed 25 minutes after the instillation of second drop of tropicamide. The subjects fixated on 6/9 (20/30) size letters on a near point card viewed at optical infinity through a +4.00 D Badal lens. Ten valid readings were obtained and the spherocylindrical values were averaged using the power vector analysis.⁵⁰

Visual Acuity

The visual acuity at distance was measured using Bailey-Lovie logMAR charts (Precision Vision; LaSalle, IL) #4 and #5 for high contrast and #6 for low contrast (10% Michelson contrast) visual acuity at 4 m. The visual acuity at near was measured using the Logarithmic Visual Acuity Chart 2000 “New ETDRS” near visual acuity chart (Precision Vision; LaSalle, IL) at 40 cm. The Sekonic L-508 Zoom Master (Sekonic, Tokyo, Japan) light meter was used to calibrate all visual acuity charts to 75 to 120 cd/m². Subjects read the first letter of each line until missing one letter, then began two lines above and read every letter of every line until three or more letters were missed. LogMAR visual acuity was calculated from the total number of letters correctly read.

During the baseline visit, monocular and binocular high contrast distance visual acuity, binocular low contrast distance visual acuity, and binocular high contrast near visual acuity were tested when the subjects wore his/her best-corrected manifest refraction in a trial frame. Binocular high contrast near visual acuity was also measured when the subjects wore their +2.50 D add soft contact lenses with the spherical over-refraction in a trial frame. During the 3-week visit and subsequent visits, best-corrected binocular visual acuities for high contrast at distance, low contrast at distance, and high contrast at near were tested when the subjects wore his/her habitual correction with the spherical over-refraction. The contact lens prescription was updated at the end of each visit if the over-refraction was greater than −0.50 D, or if the change was deemed to be clinically necessary.

Pupillometry

The NeurOptics VIP-200 Pupillometer (NeurOptics, Irvine, CA) was used to measure the pupil diameter (one reading) of the right eye under both photopic (about 190 – 250 lux) and mesopic (about 0.50 – 0.75 lux) lighting conditions.

Axial and Peripheral Eye Length

Axial (right and left eye) and peripheral (right eye only) eye length were measured under cycloplegia using the Lenstar LS 900 (Haag-Streit USA, Mason, OH).^{51, 52} Axial length was measured centrally while the subject fixated an internal, red LED (Light-Emitting Diode)

light with the eye being measured. Peripheral eye length was measured at 30° in nasal and temporal peripheral gazes. The subject was instructed to rotate his/her right eye (keeping head straight ahead) to fixate the small peripheral targets located on the instrument head at 30 degrees nasal and temporal to primary gaze. The contralateral eye was covered with an eye patch for the measurements of axial and peripheral eye length. The central and peripheral measurements were repeated until five reliable readings were obtained without red highlights that indicate poor-quality readings.

Peripheral Refractive Error

Peripheral refractive error (without the contact lens) was measured in the right eye at 30° in nasal and temporal gazes using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL); the left eye was covered with an eye patch. The subject was instructed to rotate his/her head (eye in primary gaze) until fixating a peripheral target, which were spots on the wall created by a laser pointer at 30 degrees nasal and temporal to primary gaze.

Peripheral Defocus

Peripheral defocus with the contact lens was performed at 30° in nasal and temporal gazes, at both distance and near, using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL). The left eye was covered with an eye patch, and the subject was instructed to rotate his/her head (eye in primary gaze) until fixating a peripheral target. The distance targets were spots on the wall created by a laser pointer and near targets were 2.06 M size letters (20/125 Snellen Equivalent) placed at 33 cm. Both distance and near targets were presented peripherally at 30 degrees nasal and temporal to primary gaze.

Accommodative Lag

Accommodative lag was evaluated on the right eye using the Grand Seiko WAM-5500 Binocular Autorefractor/Keratometer (AIT Industries, Bensenville, IL) while subjects viewed a 4 X 4 grid of 20/125 Snellen Equivalent letters at a distance of 33 cm.⁵³ The subject's left eye was occluded during the measurement and accommodative lag was calculated as the dioptric differences between the accommodative response and stimulus.⁵⁴ Subjects wore their best corrected spherical equivalent of the manifest refraction in trial frame for baseline measurement and their habitual soft contact lens correction for measurements at 3-week visit and subsequent visits.

Near Phoria

Phoria at near was measured using the Modified Thorington test through the phoropter. The Modified Thorington test was used because it is repeatable and easy for children to understand.^{55, 56} The subject wore his/her manifest refraction at baseline visit and habitual contact lenses with over-refraction on the phoropter at annual visits for the measurement. A horizontal Maddox rod was added in front of the right eye of the subject for 30 seconds before testing to eliminate both fast and slow vergence effects⁵⁷ and to allow for manifestation of the full phoria. A near Muscle Imbalance Measure (MIM) card with a pen

light behind shining through the hole in the center of the card was attached to the phoropter at 40 cm from the subject. The subject was instructed to report which side of the card and the number the red line they see went through on the MIM card. A positive value indicates esophoria, and a negative value indicates exophoria.

Slit Lamp Examination

Slit lamp examination was performed at each visit to evaluate contact lens fit and ocular health. The Efron Grading Scales were used to grade conjunctival redness, limbal redness, corneal neovascularization, corneal staining, papillary conjunctivitis, blepharitis, Meibomian gland dysfunction, and corneal infiltrates.⁵⁸ Grading for contact lens movement included: extremely inadequate (no movement), slightly inadequate (<0.2 mm), optimum (0.2–0.4 mm), slightly excessive (0.4–1.0 mm), and extremely excessive (>1.0 mm). Grading for contact lens centration included: optimum, slightly decentered (no limbal exposure), and extremely decentered (limbal exposure). Grading for lens movement upon push-up included: excessive, unacceptable; moderate, acceptable; optimum; minimal, acceptable; and insufficient, unacceptable.

Convergence Insufficiency Symptom Survey

The Convergence Insufficiency Symptom Survey was administered to evaluate the symptoms related to presumed binocular problems, and a total score of 16 or higher indicated symptomatic convergence issues. If the score was 16 or higher, a further evaluation of binocular vision was performed; and if necessary, the patient was referred to the Binocular Vision and Pediatric clinic at the OSU College of Optometry for treatment, but he/she would not be excluded from the study.

Choroidal Thickness

Optical Coherence Tomography (OCT) images of the choroid were obtained at 1-week visit, 2-week visit, and all annual visits. The choroidal images were captured by Spectralis Spectral Domain OCT (SD-OCT; Heidelberg Engineering, Heidelberg, Germany) with enhanced depth imaging (EDI) capabilities.^{39, 40, 59–63} OCT images were collected only in the right eye through a non-dilated pupil, and the left eye was covered with an eye patch. All OCT images were taken immediately after removing the child's study contact lenses due to previous reports that choroidal thickness changes rapidly in response to changes in optical defocus.^{39, 40} OCT images were obtained in central gaze, and the subjects were instructed to look straight ahead into the instrument at the blue light. Automatic Real-Time (ART; 30 frames) mode was turned on, and EDI mode was activated to enhance the contrast of choroidal images. The OCT was set in High Resolution (HR) mode with a scan width of 1536 A-scans. The scans were in Star pattern, and 6 sections of scans were performed automatically with section separation angle of 30 degrees for each image acquisition. The OCT image of the choroid obtained at 1-week visit was set to be as the reference image, which was then used in the "Follow-Up" mode for all subsequent choroidal imaging to maximize instrument repeatability. The OCT images were then exported for segmentation using a custom software (Duke Optical Coherence Tomography Retinal Analysis Program, DOCTRAP⁶⁴) developed in MATLAB (Mathworks, Natick, MA). The DOCTRAP Software performs custom semi-automated routines that implements automated segmentation of the

choroidal images, with optional manual adjustments of the segmentations.⁶³ The DOCTRAP segmentation output was then processed using custom MATLAB algorithms to calculate choroidal thickness.

Statistical Analyses

The comparability between eligible and ineligible subjects at baseline was assessed by the Chi-square or Fisher's exact test for categorical variables or Student's t-test for continuous variables. Percentage of atropine use during the run-in period was assessed by three different methods: self-reported calendars, parental surveys, and weight of atropine bottle. Repeated measures analysis of variance (ANOVA) was used to compare these three different methods. Paired t-tests were used to compare the data of visual acuity, accommodative lag, near phoria, pupil size, and CISS score between baseline and the 3-week visit. Regression analyses were performed to investigate factors that might be associated with pupil size, including race of the subjects and time of day when the pupil sizes were measured.

RESULTS

The BLINK Study is an ongoing three-year randomized clinical trial; therefore, data from that investigation cannot be examined by treatment group and the +2.50-D add and single vision control group subjects cannot be matched until completion of the BLINK Study.⁴⁴ For that reason, this article presents results only for the subjects who received combination treatment of soft bifocal contact lenses and 0.01% atropine in the BAM Study.

Between August 2, 2016 and April 4, 2017, a total of 73 subjects participated in baseline visits, and 49 subjects were enrolled in the BAM Study. The proportion of children who were willing to participate but ineligible for the BAM Study (32.9%) was similar to that of the BLINK Study (33.6%). The main reasons for ineligibility included myopia out of range ($n = 11$), could not agree to participate for 3 years ($n = 6$), and astigmatism too high ($n = 3$). Three of the ineligible subjects were initially eligible but were lost to follow-up during the run-in period and therefore not enrolled in the study.

No significant differences were detected between eligible and ineligible subjects ($P > .05$) for any of the demographic variables (Table 3) or outcome measures (Table 4) for the BAM Study. Approximately 55% of the enrolled subjects were females, and approximately 84% of the subjects were 9 years or older (mean = 9.6 ± 1.4). The range of spherical equivalent cycloplegic autorefraction was -0.91 to -4.83 D (mean = -2.33 ± 1.03), and astigmatism ranged from $+0.43$ to -0.41 for J_0 and from $+0.26$ to -0.38 for J_{45} .

During the run-in period (between 1-week and 3-week visit), enrolled subjects finished $93.1 \pm 7.2\%$ of atropine based on self-reported results marked on the calendars, $92.1 \pm 10.1\%$ of atropine based on the survey results completed by parents, and $93.4 \pm 9.1\%$ of atropine eye drops based on weight, respectively. Repeated measures ANOVA revealed no significant differences in the percentage of atropine use based on the three methods ($F_{(2, 96)} = 0.47$, $P = .57$). Surveys completed by parents indicated the subjects wore soft bifocal contact lenses $77 \pm 22\%$ of waking hours and used 0.01% atropine 6.4 ± 0.7 days per week between the time period of baseline and 3-week visit.

Table 5 shows the comparison of visual acuity and vision-related outcomes between baseline and at 3-week visit for the BAM Study. After two weeks of treatment with 0.01% atropine and soft bifocal contact lenses, the best-corrected high-contrast visual acuity at distance was not significantly different from baseline (-0.02 ± 0.07 for both; $P = .44$), whereas the best-corrected low-contrast visual acuity at distance was about a half line worse than baseline (baseline = $+0.09 \pm 0.07$, 3-week visit = $+0.16 \pm 0.08$; $P < .0001$). The best-corrected high-contrast visual acuity at near was not significantly different between pre- and post-treatment (baseline = -0.08 ± 0.07 , 3-week visit = -0.07 ± 0.08 ; $P = .39$). Although the Modified Thorington test revealed significantly more exophoria following treatment with atropine and soft bifocal contact lenses (baseline = -0.5 ± 6.9 , 3-week visit = -2.7 ± 6.7 ; $P = .01$), the change was approximately 2 (mean = 2.2 ± 5.8 ; range = -17 to $+19$) and the average exophoria was less than 3 after the treatment (range = -19 to $+13$). Despite the small increase in exophoria, the accommodative lag did not change significantly (baseline = 1.34 ± 0.45 D, 3-week visit = 1.40 ± 0.54 D; $P = .62$). In addition, the Convergence Insufficiency Symptom Survey Score at the 3-week visit was significantly better than the baseline score (baseline = 13.10 ± 7.89 , 3-week visit = 8.55 ± 6.62 ; $P < .0001$). Interestingly, the pupil size was not significantly different between pre- and post-treatment for either the photopic (baseline = 5.43 ± 0.65 , 3-week visit = 5.40 ± 0.70 ; $P = .74$) or mesopic condition (baseline = 6.62 ± 0.63 , 3-week visit = 6.58 ± 0.56 ; $P = .53$). Linear regression analyses revealed that pupil sizes were not significantly correlated with race of subjects or time of day when the pupil sizes were measured for either photopic or mesopic condition ($P > .05$).

Surveys completed by subjects at the 3-week visit indicated good vision, comfort, and satisfaction with contact lens wear. With a scale of 1 being poor and 10 being excellent, 94% of subjects rated the overall satisfaction with their contact lenses as a score of 8 or higher, 90% of subjects rated their vision during the day 8, and 82% of subjects rated their vision during the night 8. Using the same scale, the comfort of their eyes during the day and during the evening were both rated 8 by 80% of subjects. With a scale of 1 being difficult and 10 being easy, 94% of subjects rated the difficulty of taking out their contact lenses as a score of 8 or higher, while only 45% of subjects rated the difficulty of putting in their contact lenses 8.

Surveys regarding atropine side effects completed by parents at the 3-week visit showed that 55% of subjects complained to their parents about eye itching, burning, or stinging when putting drops in the eyes or eye irritation at the application site, with 70% of these subjects rated the severity as mild, 30% as moderate, and none as severe; 46% of these subjects rated the frequency as infrequently or sometimes, and 54% as fairly often or always. One subject also experienced infrequent eye pain with mild severity. In addition, two subjects reported mild fever, two subjects experienced mild flushing or dryness of the skin, and two subjects reported mild skin rash, hives, or itching; the frequency of these events was infrequently or sometimes. None of the symptoms were severe enough to warrant discontinuing atropine use or to be categorized as adverse events.

DISCUSSION

No previous study has reported the myopia control effects for a combination treatment of atropine and soft bifocal contact lenses, and to our knowledge, the BAM Study is the first to combine 0.01% atropine and soft bifocal contact lenses. The enrolled subjects in the BAM Study were 7 to 11 years old at baseline, which overlaps the age range of the other myopia control studies that involved soft bifocal contact lenses and atropine.^{10–13, 29–31, 36, 37, 44, 65} The range of spherical equivalent myopia was -0.75 to -5.00 D, which was also similar to the other myopia control studies.

Subjects were compliant with the two weeks of combination treatment of 0.01% atropine and soft bifocal contact lenses and tolerated the treatment well. Two weeks of combination treatment reduced best-corrected low-contrast visual acuity at distance, but did not have an effect on high-contrast visual acuity at near or distance. Chia and colleagues found that the best-corrected high-contrast visual acuity at distance and near was not affected by the use of 0.01% atropine in children aged 6–12 years with myopia.²⁹ Similarly, Loughman and Flitcroft found that high-contrast visual acuity at distance and near were not adversely affected by 0.01% atropine among young adults.⁶⁶ Neither study evaluated low-contrast visual acuity. Several studies that involved multifocal contact lens designs with add power of $+2.50$ D or less found no difference in high-contrast visual acuity when compared to either spectacles or spherical contact lenses,^{10, 65, 67, 68} although Kang et al. reported a statistically significant decrease in high- and low-contrast visual acuities when using lenses with add power of $+3.00$ D.⁶⁸ The BLINK Study, which fitted children with the same type of multifocal contact lenses as BAM Study (Biofinity Multifocal “D”; $+2.50$ D add), found no difference in best-corrected high-contrast visual acuity when compared to spectacles ($P = .59$); data of low-contrast visual acuity were not available at the time of publication.⁴⁹

Previous studies found that 0.01% atropine had a negligible effect on accommodation among children and young adults,^{29, 30, 66} although it was reported that wearing soft multifocal contact lenses led to more exophoria and reduced accommodative responses in children.⁶⁹ In the BAM Study, the combination treatment over two weeks induced more exophoria at near, but the amount (about 2° on average) was not clinically significant. The CISS scores improved significantly despite the small increase in exophoria, possibly due to regression towards the mean or placebo effect. In addition, the accommodative lag did not change significantly from baseline. The infrared beam size of the Grand Seiko autorefractor is only about 2 mm in diameter,⁷⁰ while the optical zone of the Biofinity soft bifocal contact lens is 3 mm.⁷¹ Therefore, it's reasonable to assume that the autorefraction readings reflect the subject's accommodative response/lag if the lens is well centered, although it should be treated with caution when interpreting the results as the autorefraction readings may include the add power of the contact lenses during measurements.

The findings that the pupil size did not change after two weeks of combination treatment for either the photopic or mesopic condition were inconsistent with previous studies that involved 0.01% atropine. In the study conducted by Chia et al among Asian children aged 6–12 years, the pupil size increased by about 1 mm after two weeks of 0.01% atropine treatment (administered once nightly) for both of the photopic (3.9 ± 0.6 mm vs 5.2 ± 0.8

mm) and mesopic (4.7 ± 0.7 mm vs 5.8 ± 0.8 mm) conditions.²⁹ In another study conducted among Caucasian adults aged 18–27, the pupil size increased significantly by about 1 mm after receiving one drop of 0.01% atropine daily for 5 days.⁶⁶ We did not find significant correlations between pupil size and race of subjects or between pupil size and the time of day when pupil size was measured for either photopic or mesopic condition, so it is unlikely to be related to differences in the racial distribution between studies or the time since the last atropine administration.

The BAM Study has several limitations. This study is supported by an NIH (National Institutes of Health) K23 Mentored Patient-Oriented Research Career Development Award, and a randomized clinical trial is not possible due to constraints on training grants. However, to our knowledge currently there is no study using low concentration atropine and soft bifocal contact lenses, so these data may serve as justification for a future randomized clinical trial. A historical control comparison will be made between the BAM Study group and the single vision contact lens and +2.50 D add bifocal contact lens subjects in the BLINK Study. Enrolling subjects who are age-matched to those in the BLINK Study and conducting identical protocols will help to reduce the potential for bias. A limitation of using historical control comparison is that placebo control (such as artificial tears) for 0.01% atropine in regard to treatment effects or reporting symptoms related to this study could not be obtained.

In addition, the subjects' compliance with long-term use of atropine could be a potential problem. However, the run-in period was used to ensure adequate compliance with atropine use at least over the short term. Contact lens wear was not a primary concern, as previous studies have shown that 7- to 11- year old children are capable of contact lens wear and care.^{45, 72, 73} Throughout the study, the subjects' compliance with using atropine and contact lenses will be monitored using the compliance surveys.

In summary, the BAM Study will investigate the effect of combining optical and pharmacological treatments on myopia progression. The intervention could provide significant scientific information on the combination of these myopia control treatments and potentially change the standard of care for myopia control in a clinical setting.

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Table 1.

Schedule of measurements for the BAM Study.

	Baseline	1 week	3 weeks	Semi-annual	Annual
Manifest refraction (OU)	X				X
Spherical over-refraction (OU)		X	X	X	X
High contrast VA (OU) OD/OS at baseline	X (M)		X (CL)	X (CL)	X (CL)
Low contrast visual acuity (OU)	X (M)		X (CL)	X (CL)	X (CL)
Near visual acuity (OU)	X (M)		X (CL)	X (CL)	X (CL)
Modified Thorington	X (M)		X (CL)		X (CL)
Accommodative lag and peripheral defocus with CL, near (OD)			X		X
Contact lens centration, movement (OU)	X	X	X	X	X
Choroidal thickness (OD)		X	X		X
Slit lamp examination (OU, no contact lens)	X	X	X	X	X
Pupil size (OD)	X		X	X	X
Non-cycloplegic autorefraction (OU)	X			X	X
Accommodative Lag with Manifest (OD)	X				
Cycloplegic autorefraction (1° outcome, OU) *	X				X
Peripheral refractive error without CL (OD) *	X				X
Axial length (OU) *	X				X
Peripheral eye length (OD) *	X				X
Videophakometry (OD) *	X				X
Peripheral defocus with CL (OD) *	X				X
Intraocular pressure (OU) *	X			X	X
Dilated fundus examination (OU) *	X				X

The 1-week visit occurs within ± 3 days of one week; the 3-week visit occurs within 1 week of the three-week date; all subsequent visits occur at six-month intervals ± 30 days.

* *cycloplegic measures*; X (M) = wearing manifest refraction in trial frame; X (CL) = wearing habitual contact lens; OD = right eye; OS = left eye; OU = both eyes.

Table 2.

Parameters for the primary and secondary contact lenses used in the BAM Study.

	Primary Biofinity Multifocal “D”	Backup Proclear Multifocal “D”
Material	Comfilcon A	Omafilcon A
Water Content	48%	60%
Base Curve	8.6	8.7
Diameter	14.0	14.4
Add Power	+1.50 D or +2.50 D	+1.50 D or +2.50 D
Powers	up to −10.00 (−0.50 steps > −6.00)	up to −10.00 (−0.50 steps > −6.50)
dK	128.0	34.0

Table 3.

Demographic information of eligible and ineligible subjects in the BAM Study.

	Eligible (n = 49)	Ineligible (n = 24)	P-value
Female	27 (55.1)	11 (45.8)	.46
Age (years)	9.6 ± 1.4	9.6 ± 1.2	.87
7	4 (8.2)	3 (12.5)	
8	4 (8.2)	3 (12.5)	
9	15 (30.6)	2 (8.3)	
10	12 (24.5)	8 (33.3)	
11	14 (28.6)	8 (33.3)	
Ethnicity			> .99
Hispanic or Latino	1 (2.0)	1 (4.2)	
Not Hispanic or Latino	48 (98.0)	23 (95.8)	
Race			.95
American Indian or Alaska Native	1 (2.0)	0 (0.0)	
Asian	10 (20.4)	8 (33.3)	
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	
Black or African American	1 (2.0)	1 (4.2)	
White	31 (63.3)	15 (62.5)	
More than one race	6 (12.2)	0 (0.0)	
Unknown or not reported	0 (0.0)	0 (0.0)	
Age of first glasses (years)	7.8 ± 1.3	7.5 ± 2.5	.65
Parental Myopia			
Father	31 (72.1)	13 (68.4)	.77
Mother	32 (72.7)	16 (72.7)	> .99
Near work (hours/week outside school)			
Study or read for school assignments	6.4 ± 4.3	6.6 ± 5.8	.87
Read for fun (pleasure)	6.3 ± 4.6	6.8 ± 6.3	.75
Watch television	5.6 ± 4.0	5.9 ± 4.9	.77
Use a computer	4.7 ± 4.1	5.2 ± 6.4	.73
Play video games (Xbox, PlayStation, Wii)	1.7 ± 2.5	1.5 ± 1.7	.76
Uses handheld electronic devices (iPad, Nintendo DS, etc.)	5.1 ± 4.6	6.8 ± 8.8	.40
Time spent outdoors	7.8 ± 4.3	7.8 ± 3.7	.99
Convergence Insufficiency Symptom Survey Score	13.1 ± 7.9	11.8 ± 9.3	.65

Mean ± standard deviation are presented for continuous variables and number (proportion) for categorical data. *P*-value indicates the comparison between eligible and ineligible subjects.

Table 4.

Ocular data of eligible and ineligible subjects in the BAM Study, mean $\pm$ standard deviation right eye, unless otherwise noted.

	Eligible (n = 49)	Ineligible (n = 24)	P-value
Refractive Error (D)			
Spherical Equivalent	-2.33 ± 1.03	-1.64 ± 1.21	.32
J ₀	-0.07 ± 0.18	0 ± 0.26	.18
J ₄₅	-0.05 ± 0.18	0 ± 0.23	.40
Best Corrected LogMAR Visual Acuity			
High Contrast Distance OD	-0.01 ± 0.06	$+0.02 \pm 0.09$	.30
High Contrast Distance OS	-0.02 ± 0.06	$+0.01 \pm 0.07$	.09
High Contrast Distance OU	-0.02 ± 0.07	0.00 ± 0.07	.26
Low Contrast Distance OU	$+0.09 \pm 0.07$	$+0.12 \pm 0.09$	.19
High Contrast Near OU	-0.08 ± 0.07	-0.05 ± 0.09	.15
Pupil Size (mm)			
Photopic	5.4 ± 0.6	5.3 ± 0.6	.53
Mesopic	6.6 ± 0.6	6.5 ± 0.7	.63
Simulated Keratometry (D)			
Steep Meridian	44.05 ± 1.39	Not measured	
Flat Meridian	43.37 ± 1.32	Not measured	
Biometry (mm)			
Anterior Chamber Depth	3.94 ± 0.21	Not measured	
Lens Thickness	3.32 ± 0.13	Not measured	
Vitreous Chamber Depth	17.13 ± 0.63	Not measured	
Axial Length	24.39 ± 0.62	Not measured	

P-value indicates the comparison between eligible and ineligible subjects.

J₀ = with- and against-the-rule astigmatism components; J₄₅ = oblique astigmatism components; OD = right eye; OS = left eye; OU = both eyes; D = diopter; mm = millimeter

Table 5.

Visual acuity and vision-related outcomes at baseline and 3-week visit for subjects enrolled in the BAM Study.

Visual acuity and vision-related outcomes		Baseline	3-week	P-value
Best-corrected Visual Acuity (logMAR)	High-contrast at Distance	-0.02 ± 0.07	-0.02 ± 0.07	.44
	Low-contrast at Distance	+0.09 ± 0.07	+0.16 ± 0.08	< .0001
	High-contrast at Near	-0.08 ± 0.07	-0.07 ± 0.08	.39
Near Phoria (°)*		-0.5 ± 6.9	-2.7 ± 6.7	.01
Accommodative Lag (D)		1.34 ± 0.45	1.40 ± 0.54	.62
Pupil Size (mm)	Photopic	5.43 ± 0.65	5.40 ± 0.70	.74
	Mesopic	6.62 ± 0.63	6.58 ± 0.56	.53
Convergence Insufficiency Symptom Score		13.10 ± 7.89	8.55 ± 6.62	< .0001

The subjects wore best-corrected manifest refraction in trial frame for baseline measurements and best-corrected soft bifocal contact lenses for 3-week measurements (pupil size was measured without any corrections in place).

P-value indicates the comparison between baseline and 3-week measurements.

* Negative values indicate exophoria