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Longitudinal Changes of Angle Configuration in Primary Angle-Closure Suspects

The Zhongshan Angle-Closure Prevention Trial

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Objective: To determine longitudinal changes in angle configuration in the eyes of primary angle-closure suspects (PACS) treated by laser peripheral iridotomy (LPI) and in untreated fellow eyes.

Design: Longitudinal cohort study.

Participants: Primary angle-closure suspects aged 50 to 70 years were enrolled in a randomized, controlled clinical trial.

Methods: Each participant was treated by LPI in 1 randomly selected eye, with the fellow eye serving as a control. Angle width was assessed in a masked fashion using gonioscopy and anterior segment optical coherence tomography (AS-OCT) before and at 2 weeks, 6 months, and 18 months after LPI.

Main Outcome Measures: Angle width in degrees was calculated from Shaffer grades assessed under static gonioscopy. Angle configuration was also evaluated using angle opening distance (AOD250, AOD500, AOD750), trabecular-iris space area (TISA500, TISA750), and angle recess area (ARA) measured in AS-OCT images.

Results: No significant difference was found in baseline measures of angle configuration between treated and untreated eyes. At 2 weeks after LPI, the drainage angle on gonioscopy widened from a mean of 13.5° at baseline to a mean of 25.7° in treated eyes, which was also confirmed by significant increases in all AS-OCT angle width measures ($P<0.001$ for all variables). Between 2 weeks and 18 months after LPI, a significant decrease in angle width was observed over time in treated eyes ($P<0.001$ for all variables), although the change over the first 5.5 months was not statistically significant ($P = 0.07-1.00$). In untreated eyes, angle width consistently decreased across all follow-up visits after LPI, with a more rapid longitudinal decrease compared with treated eyes (P values for all variables ≤ 0.01). The annual rate of change in angle width was equivalent to 1.2°/year (95% confidence interval [CI], 0.8−1.6) in treated eyes and 1.6°/year (95% CI, 1.3−2.0) in untreated eyes ($P<0.001$).

Conclusions: Angle width of treated eyes increased markedly after LPI, remained stable for 6 months, and then decreased significantly by 18 months after LPI. Untreated eyes experienced a more consistent and rapid decrease in angle width over the same time period. *Ophthalmology 2014;■:1−7 © 2014 by the American Academy of Ophthalmology.*

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Primary angle-closure glaucoma (PACG) predominantly presents in the form of a chronic asymptomatic condition[1−3] and is estimated to be responsible for approximately half of binocular glaucoma blindness worldwide.[4] A previous population-based study reported that more than 10% of elderly Chinese are asymptomatic suspects at risk of angle-closure.[5] A considerable proportion of angle-closure suspects are at risk of progression to primary angle-closure or PACG.[6,7] Laser peripheral iridotomy (LPI), a recognized first-line therapy for the treatment of PACG, has been demonstrated to prevent acute attacks of angle-closure in the fellow eyes of patients who have unilateral acute angle-closure.[8−10] However, no conclusive evidence has demonstrated that persons with asymptomatic narrow angles on gonioscopy benefit from prophylactic LPI. Previous studies have shown that LPI opens the drainage angle in a majority of primary angle-closure suspects (PACS), whereas angles in a significant minority of eyes remained closed after LPI.[8,11] In the context of limited healthcare resources and budgets, the efficacy of prophylactic LPI needs to be demonstrated. Furthermore, the harms (if any) of prophylactic treatment need to be determined.

Since 2008, a large-scale randomized clinical trial[12] (the Zhongshan Angle-Closure Prevention [ZAP] trial, trial registration information: http://www.controlled-trials.com/ISRCTN45213099; accessed January 26, 2014) was initiated with the purpose of assessing the efficacy and safety of

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LPI as a prophylactic measure to prevent the development of acute or chronic primary angle-closure in asymptomatic suspects with gonioscopically evident narrow drainage angles. In the current study, we analyzed the longitudinal changes in anterior chamber angle configuration of PACS eyes in the ZAP cohort. The study design of the ZAP trial (i.e., treating 1 randomly selected eye in each participant with LPI and using the fellow untreated eye as the control) provides a unique opportunity to compare the long-term change of angle configuration in eyes with and without intervention by laser treatment. This will also help evaluate the influence of LPI on the natural history of PACS.

Methods

Ethical approval was obtained from the Ethical Review Board of Sun Yat-sen University and the Ethical Committee of Zhongshan Ophthalmic Center. The study also received institutional review board approval from Moorfields Eye Hospital (via the London School of Hygiene and Tropical Medicine) and Johns Hopkins University Hospital. The study was conducted in accordance with the Tenets of the World Medical Association's Declaration of Helsinki. Study participants were recruited from a randomized controlled clinical trial, the ZAP trial (trial registration information: http://www.controlled-trials.com/ISRCTN45213099, accessed January 26, 2014). The International Standard Randomized Controlled Trial Number was issued on May 6, 2008.

All examinations and interventions were carried out in the Clinical Research Data Collection Center at Zhongshan Ophthalmic Center, a tertiary specialized hospital in Guangzhou, South China. The field procedures for this trial have been reported.[12] In brief, 11 991 Guangzhou citizens aged between 50 and 70 years participated in the screening survey from September 2008 to August 2010. Primary angle-closure suspects eligible for this study were defined as those who had 6 or more clock hours of angle circumference in which the posterior/pigmented trabecular meshwork was not visible under static gonioscopy in both eyes, without intraocular pressure (IOP) elevated to >21 mmHg, no peripheral anterior synechiae, no glaucomatous optic neuropathy, and no evidence of anterior segment ischemia from a previous acute IOP increase. All participants underwent a darkroom prone provocative test as part of the enrollment tests. Those who had an IOP increase greater than 15 mmHg above baseline during darkroom prone provocative test were excluded. All eligible participants received LPI in 1 randomly selected eye, with the fellow eye serving as a control. Randomization was carried out using a pregenerated list of random numbers. Each eligible participant was assigned a number according to his/her sequence of entering the study. Randomization numbers and their corresponding eye assignment were generated at the data-monitoring center at Wilmer Eye Institute and sent in sealed envelopes to the clinical data-collection center at Zhongshan Ophthalmic Centre.[12]

Detailed information on all examinations in the ZAP trial has been reported.[12] The limbal anterior chamber depth was assessed under slit-lamp microscopy using a modified van Herick grading scheme.[13] The IOP was measured using Goldmann applanation tonometry (Haag-Streit AG, Koeniz, Switzerland). The median of 3 readings for each eye was considered. Ocular biometric measures (i.e., axial length, central anterior chamber depth, and lens thickness) were acquired using ultrasound A-scan (CineScan A/B, Quantel Medical, Bozeman, MT). The width of the anterior chamber angle was assessed using both evaluation under static gonioscopy and quantitative measurements from images acquired by anterior segment optical coherence tomography (AS-OCT).

Gonioscopy

Static gonioscopy was performed using a Goldmann-type, 1-mirror gonioscopic lens (Haag-Streit AG) with low ambient illumination and a 1-mm narrow beam. Gonioscopic examinations were carried out by specialist-trained ophthalmologists (Y.J., S.H.) with high intergrader agreement (weighted kappa values for all variables >0.80).[12] Gonioscopy was performed in a standardized dark room with low ambient illumination (<1 lux illumination by digital light meter (measured using the Easy View model EAQ30; Extech Instruments, Inc, Waltham, MA)) at all study visits by an examiner who was masked to the findings collected at other visits. Care was taken to avoid the beam falling on the pupil to prevent alteration of the angle configuration. If trabecular meshwork could not be seen because of marked iris convexity, an "over the hill" view was obtained by slightly tilting the lens toward the trabecular meshwork without causing corneal indentation. Angle width was assessed under static gonioscopy using the Shaffer grading system: The width of anterior chamber angle in each quadrant was estimated as the angle in degrees between a tangent line to the surface of the trabecular meshwork and another tangent line to the peripheral third of the iris, and then was recorded in 5-point categories (Shaffer grades 0 to 4 correspond to 0°, 10°, 20°, 30°, and 40°, respectively). The range of iridotrabecular appositional contact observed under static gonioscopy was recorded. Peripheral iris profile was evaluated under gonioscopy and classified as being regular, steep, plateau, or queer.[14]

Anterior Segment Optical Coherence Tomography

Horizontal and vertical scans of AS-OCT (Visante, Carl Zeiss Meditec, Dublin, CA) were performed to obtain images of the anterior chamber angle in 4 quadrants. The AS-OCT scans were carried out in the same standardized low ambient illumination at all study visits.

The AS-OCT images were quantitatively assessed using custom software (the Zhongshan Angle Assessment Program[15]) to measure angle opening distance (AOD), trabecular-iris space area (TISA), and angle recess area (ARA). Image analysis was performed by 3 certified graders who were masked to the intervention assignment and study visit. A set of 200 images from 200 eyes were randomly selected and graded by all 3 graders independently. Good intergrader agreement was shown by high intraclass correlation coefficient (0.77−1.00). The AOD was defined as the length of a line drawn from the anterior surface of the iris to the corneal endothelial perpendicular to the plane of the surface of the trabecular meshwork at 250 μm, 500 μm, and 750 μm from the scleral spur (AOD250, AOD500, and AOD750, respectively).[16] The TISA was defined as the trapezoidal area between anteriorly, AOD500 and AOD750 (TISA500 and TISA750, respectively); posteriorly, a line drawn from the scleral spur perpendicular to the plane of the inner scleral wall to the anterior surface of the iris; superiorly, the inner corneoscleral wall; and inferiorly, the anterior surface of the iris.[17,18] The ARA was defined as the triangular area between the anterior iris surface, the inner corneoscleral wall, and a line perpendicular to the AOD750.[18] Iris curvature (alternatively named "iris convexity") was defined as the maximum perpendicular distance between the posterior iris surface and the line connecting the most peripheral and the most central points of iris pigment epithelium relative to the pupillary center. The IT750 was defined as perpendicular iris thickness measured at 750 μm from the scleral spur. Mean pupil diameter of the horizontal and vertical scans acquired in the dark was recorded for each eye. Lens vault, defined as the perpendicular distance between the anterior pole of the crystalline lens and the horizontal line joining the 2 scleral spurs,[19] was measured using AS-OCT images.