Efficacy of Laser Peripheral Iridotomy for the Prevention of Angle Closure: A Randomized Controlled Trial

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Summary

Background: Primary angle-closure glaucoma (PACG) affects 20 million people worldwide. People classified as primary angle closure suspects (PACS) have a higher but poorly quantified risk of developing glaucoma. Laser peripheral iridotomy (LPI) is widely practiced as prophylaxis against PACG but its efficacy is unproven.

Methods: In this randomized controlled trial, 11,991 participants aged between 50 and 70 years were screened in the community from Guangzhou, China. People with bilateral PACS were enrolled and received LPI in one randomly selected eye, with the fellow remaining untreated. The primary outcome was incident primary angle closure disease as a composite endpoint of elevation of intraocular pressure, or peripheral anterior synechiae, or acute angle-closure during 72 months of follow up.

Findings: Of the 889 subjects who underwent randomization, 889 treated and 889 untreated eyes were included in the intention-to-treat analysis. The incidence rate of primary outcome was 4.2 per 1,000 eye-years in treated eyes versus 8.0 per 1,000 eye-years in untreated eyes (HR 0.53, 95%CI: 0.30–0.92). A primary outcome event occurred in 19 treated eyes and 36 untreated eyes with a statistically significant difference using pair-wise analysis (p=0.004). No serious adverse events were observed during follow up.

Interpretation: The risk of incident angle-closure disease was very low among individuals with PACS identified through community-based screening. LPI had a modest, albeit significant, prophylactic effect. In view of the low incidence rate of outcomes that have no

immediate threat to vision, the benefit of prophylactic LPI is limited and thus it should only be offered to those with the highest risk of PACG. **(**ISRCTN45213099).

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Introduction

Glaucoma is the world's most common neurodegenerative disease affecting around 80 million people. It is the second most common cause of blindness.[1] Primary angle-closure glaucoma (PACG) accounts for 25% of all glaucoma globally and it is more visually destructive than the more common variant, primary open angle glaucoma. Over three quarters of those with PACG live in Asia, and 3.1 million Chinese citizens are blind in at least one eye from PACG.[2 3] It is assumed that PACG develops from a larger group of people in whom the drainage of aqueous humor from the eye is impeded by narrowing of the outflow channels in the anterior chamber angle. Individuals in whom half the outflow channels appear obstructed are considered to be at high risk. These people are termed primary angle closure suspects (PACS). Angle closure can be caused by many factors including the location of the lens, iris thickness and insertion, ciliary body location and degree of pupil block.[4] Primary angle-closure (PAC) is an intermediate stage in which ocular anatomy and physiology of the trabecular meshwork are obstructed by the peripheral iris, but vision is normal.[4] It has been estimated there are over 28 million people with PACS, 9 million with PAC, and 4.5 million with PACG in China alone.[2]

Laser peripheral iridotomy (LPI) has been the first-line treatment for PAC and PACG since the mid 1970's.[5] LPI is mandatory in "acute angle closure" (AAC), a clinical variant presenting with florid symptoms.[6] Although widely practiced, evidence for prophylactic LPI in PACS is lacking. In the United States nearly 50,000 LPI procedures are performed annually.[7] In the UK, with 31.1 million people aged 40 years and older,[8] incident AAC and/or

PACG occurs at around 4 per 100,000/annum (around 1250 cases per year).[9] In 2014-15, 10,284 laser iridotomies were performed in the UK National Health Service (NHS), suggesting many were for early stage disease (most likely PACS).[10] 75% of UK consultant ophthalmologists surveyed in 2000 offered prophylactic LPI.[11] In China, with 28 million PACS cases, the question of prophylactic treatment raises important questions around health economics, opportunity costs and public health policy. One randomized trial of screening and prophylactic LPI for individuals with PACS carried out in Mongolia reported no benefit in prevention of sight loss from glaucoma, although this study suffered significant loss to follow-up.[12 13] The natural history of PACS is poorly documented due to the lack of long-term observational data.

Although widely practiced, the efficacy and safety for prophylactic LPI is unclear. The aim of this trial was to assess the efficacy of LPI in preventing the development of PAC or AAC in Chinese people with PACS. Meanwhile, the untreated eyes allowed us to observe the natural history of PACS since no intervention was applied to these eyes.

Methods

The full study protocol and planned statistical analysis of this trial have been published.[14]

Study Design, Participants, and Setting

The Zhongshan Angle Closure Prevention (ZAP) Trial is a single-center, randomized interventional controlled trial. All examinations and interventions were carried out in the Clinical Research Center at Zhongshan Ophthalmic Center, a tertiary specialized hospital in Guangzhou, China. This trial was approved by the Ethical Review Board of Sun Yat-Sen University and the Ethical Committee of Zhongshan Ophthalmic Center, and by the Moorfields Eye Hospital (via the London School of Hygiene and Tropical Medicine) and Johns Hopkins University institutional review boards. This trial was performed in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects before enrolling. The trial was supervised by an independent data monitoring and safety committee, an independent trial steering committee, and an independent advisory committee.

Participants aged between 50 and 70 years from an urban district in Guangzhou were invited to receive a screening examination to identify eligible subjects. Individuals presenting as bilateral PACS were enrolled. PACS was defined as angle closure (6 or more clock hours of angle circumference in which the posterior, usually pigmented, trabecular meshwork was not visible under non-indentation gonioscopy), in the absence of PAC or PACG. Specifically, there were no peripheral anterior synechiae (PAS) on gonioscopic exam and the intraocular pressure was ≤ 21mmHg (two standard deviations above the norm for urban Chinese populations).[4] The optic nerve was assessed by an ophthalmologist. Eyes were eligible if vertical cup to disc ratio (vCDR) was less than 0.7, vCDR, cup-to-disc asymmetry was no

greater than 0.2, and neuroretinal rim width was greater than 0.1 vertical disc diameter with reference to standard photos. Standard automated perimetry was performed on all enrolled subjects and normal or borderline glaucoma hemifield test results were required. Exclusion criteria included severe health problems resulting in a life expectancy of less than 1 year, prior intraocular surgery or penetrating eye injury, media opacity preventing LPI, best corrected visual acuity worse than 20/40, or an IOP increase greater than 15 mmHg after dilation or after a 15-minute dark room prone provocative testing (DRPPT). Recruitment was by means of flyers and television advertisements offering free eye examinations.

Randomization, Concealment, and Masking

All eligible subjects were allocated to receive LPI in one randomly selected eye, with the fellow eye serving as an untreated control. A pre-generated list of random numbers was used to perform randomization. Each eligible participant was assigned a number according to their sequence of entering the study. Randomization numbers and their corresponding eye assignment were generated at the data monitoring center at Wilmer Eye Institute, Baltimore, MD. The random number was kept in a sealed envelope with the corresponding sequential number written on the cover and sent to the clinical data collection center at Zhongshan Ophthalmic Center. The envelope was opened by a masked research nurse prior to LPI treatment.

Interventions

LPI was performed by a trained doctor, per a standard clinical protocol, with the use of an Abraham lens (Ocular Instruments, Bellevue, WA). 15 minutes after one drop of brimonidine 0.15% and pilocarpine 2%, a YAG laser machine (Visulas YAG III, Carl Zeiss Meditec, Dublin, CA, USA) was used to create an iridotomy starting with an initial setting of 1.5 mJ and titrating as needed to create a patent iridotomy of at least 200 μm in diameter. Wherever possible, the LPI was placed in a crypt or other area where the iris appeared thinnest and was positioned beneath the superior lid. All subjects received dexamethasone 0.1% eye drops hourly for 24 hours and then four times daily for one week after the LPI.

Outcome Measures

Both treated and untreated eyes were examined on follow-up visits after 2 weeks, 6 months, 18 months, 36 months, 54 months, and 72 months. The primary outcome was the incidence of primary angle closure by eyes, defined as the composite of three study endpoints including: (1) IOP measurements above 24 mmHg on two separate occasions; or (2) development of at least one clock hour of PAS in any quadrant; or (3) an episode of acute angle closure. Secondary outcomes included presenting visual acuity, IOP, total angle width on gonioscopy, and any adverse events during LPI or at any follow-up visits. While we monitored for the development of glaucoma, it was thought to be unlikely to occur in a substantial number of enrolled participants and therefore was not used as a study endpoint.

Gonioscopy was performed in a standardized dark environment with low ambient

illumination (<1 lux illumination) at all study visits. Static gonioscopy was performed using a Goldmann-type, one-mirror gonioscopic lens (Single Mirror Gonioscope, Ocular Instruments, Bellevue, WA, USA) with a 1mm narrow beam. Angle width was assessed under static gonioscopy using the Shaffer grading system: the width of the 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). Sometimes the iris is bowed forward making visualization of the angle quite challenging and in many of these eyes the angle is open. We allowed slight tilting of the gonioprism towards the angle being examined. We did not allow for greater manipulation as this could lead to compression opening the angle. If trabecular meshwork was not visible using the single mirror lens, a dynamic examination with a 4-mirror gonioscope (Sussman Four Mirror Gonioscope, Ocular Instruments, Washington, USA) was carried out to determine if PAS were present. If iridotrabecular contact was reversible with compression gonioscopy (i.e. could be opened and no PAS), the subject was considered to be PACS and was eligible to be included in the study. Gonioscopy was performed by glaucoma specialists after training to achieve standardization (weighted kappa values for all gonioscopy variables > 0.80 were achieved). If eyes were determined to have reached a primary endpoint, gonioscopic exam was confirmed by a senior glaucoma specialist (MGH or PJF).

Presenting visual acuity was evaluated for each eye under standard lighting conditions using the Early Treatment Diabetic Retinopathy Study (ETDRS) logarithm of the minimum angle of resolution (logMAR) E chart (Precision Vision, Villa Park, IL). The IOP was measured by non-contact tonometry (Topcon CT-80A, Tokyo, Japan) first, and those with IOP more than 24 mmHg in either eye underwent Goldmann applanation tonometry (GAT) to confirm IOP elevation. The limbal anterior chamber depth (LACD) was evaluated by a modified van Herick grading system using a slit lamp (BQ-900, Haag-Streit, Switzerland). LACD was graded clinically, with reference to standard photographs, as the depth of the temporal anterior chamber at the corneo-scleral junction, expressed as a percent of the adjacent corneal thickness. Tropicamide 0.5% and phenylephrine 5% were used to dilate the pupil for clinical examination of the lens, disc, macula and retinal periphery at baseline and each follow-up visit. Cataract was graded using the Lens Opacity Classification System III (LOCS III) with reference to standard photographs. It consists of six slit lamp images for grading nuclear color and nuclear opalescence, five retro-illumination images for grading cortical cataract, and five retroillumination images for grading posterior subcapsular cataract. Any adverse events were recorded in case-report forms and sent to the data monitoring and safety committee.

Statistical analysis

The sample size was calculated for our primary outcomes at 36 months based on previous reports stating a 3-year incidence of endpoints near 20%.[15] Assuming the total incidence of

progression to endpoint over three years of 18% (equivalent to 6% annual rate) in untreated eyes and an attrition rate up to 20%, a final target of sample size of 700 individuals was established, which had 80% power with a two-sided error (α=0.05) to detect a difference of 30% in incidence of the study endpoint in 36 months' follow-up. In the sample size estimation, we did not take into account the pair-wise statistics, such as McNemar's test, because the discordant rates among treated and untreated eyes were unknown. Considering a possible eligible rate of 10% or lower in the screening survey, we planned to recruit approximately 10,000 citizens aged 50-70 to undergo screening examinations.

An independent biostatistics and data monitoring center was set up at the beginning of the study. The ZAP database was transferred to the data monitoring center on a weekly basis. The data monitoring and safety committee met annually for a comprehensive review of the data and to provide recommendations. At the annual data monitoring meeting prior to all subjects completing the 18-month follow up visit, the decision was made, approved by all members, to extend the study from 36 months to 72 months and enroll additional 155 participants given the much lower than predicted event rate. The expected event rate had been based on a small published literature on similar patients. Since LPI was (and is) often being recommended to persons with PACS it was felt to be of value to continue the study to determine the overall harms and benefits of this practice. Further, there was reason to believe that early events in the treated eyes may have been related to the iridotomy itself (dispersion

of pigment and inflammation) and therefore outcome might be different over time. Given this interim analysis, we adjusted the *p*-value to 0.025 for significance threshold.

All analyses were based on intention-to-treat (ITT) principle and included all participants who underwent randomization. Participants who prematurely received LPI in control eye but did not withdraw from the study were followed and analyzed according to randomization (n=24). Data from those who underwent cataract surgery were censored at the last visit before cataract surgery.

The prophylactic effects were expressed in pair-wise analyses of the primary outcome using McNemar's test given randomization was at eye-level within an individual to account for inter-eye correlation. Hazard ratios (HR, with 95% CIs), were also estimated using a Cox proportional hazards model between treated and untreated eyes. The Cox proportional model was chosen as an additional analysis because it took into account both time and event, a small number of subjects contributed different follow-up time between two eyes, i.e., one eye developed endpoint but not the fellow eye, or only one eye was censored due to cataract surgery. We used Kaplan-Meier failure curves to display event rates and log-rank tests to test for equality of failure curves. Outcome measurements were compared by the paired t test for continuous variables, McNemar's test for nominal variables and Wilcoxon signed test for ordinal variables (LACD score). All statistical analyses were conducted using Stata 13.1

(StataCorp LP, College Station, TX). The significance level was set at 0.05 using a two-side test. This trial is registered with number ISRCTN45213099.

Role of the funding source:

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. DSC, BM, MH, PJF and DSF had access to all the data in the study. MH, PJF and DSF had final responsibility for the decision to submit for publication.

Results

A total of 11,991 Chinese individuals aged 50 to 70 underwent screening assessment starting on 1st June 2008. Of the 1,087 identified as eligible bilateral PACS, 188 declined participation in the trial and 889 eligible subjects were enrolled. These people were treated by LPI in a randomly selected eye leaving the fellow eye untreated as a control (Figure 1). The recruitment was completed in October 2010. The study was completed on Nov 6th, 2016, which provides sufficient time to have 72 month follow-up visits for all the participants.

The mean age was 59.3±5.0 years, with 737 (82.9%) females. The LPI-treated eyes consisted of 445 (50.1%) right eyes and 444 (49.9%) left eyes. 79% of LPIs were placed superiorly, and the rest were placed either nasally or temporally.

The baseline demographic measures, IOP, visual acuity, LACD, Shaffer grades, and cup to disc ratio in the eyes of subjects included and refusals, as well as the baseline characteristics between the LPI-treated and control eyes were similar, including IOP, ocular biometric parameters, angle width, visual acuity, and IOP elevation after dark-room prone provocative test results (Table 1).

Mean follow up for this study was 61.1±20.2 months, 61.2±20.3 months for treated group and 61.0±20.1 for control group; 74.8% (665/889) in the treated group and 74.7% (664/889) of the controls completed the study. A total of 24 control eyes received LPI during the course of the study.

During the 72 months' follow-up, 19 LPI-treated eyes and 36 control eyes reached study endpoint, with a corresponding cumulative incidence of 4.19 (95% confidence interval, 2.67 – 6.57) per 1,000 eye-years for treated eyes and 7.97 (95%CI 5.75 – 11.0) per 1,000 eye-years for control eyes (Table 2*).* To account for inter-eye correlation we analyzed the primary outcome using McNemar's test and the prophylactic effect of LPI remained significant (p=0.004, Table 3) in the pair-wise comparison between treated and untreated eyes. A primary outcome event occurred in both eyes in 10 subjects (1.1%), in the treated eyes in 9 subjects (1.0%) and in the untreated eyes in 26 subjects (2.9%). We conducted sensitivity analysis by excluding those who did not complete the study, and the findings remained statistically significant (Table S2).

We also analyzed the primary outcome using Cox proportional hazard model to account for unequal follow up time between two eyes. The LPI-treated eyes had a 47% reduction in the risk of reaching an endpoint (HR 0.53, 95% CI 0.30–0.92; *p*=0.024; Figure 2). However, the proportional hazard assumption only held through 36 months of follow up and there was no protective effect of LPI at that point (HR: 0.90, 95% CI 0.44-1.85, *p*=0.777). The hazard ratio remained similar at 72 months after adjusting for age, gender, baseline intraocular pressure and angle width (HR 0.52, 95% CI 0.30-0.91, *p*=0.023, Table 4). Eyes with narrower angle width at baseline were more likely to develop a study endpoint, but baseline intraocular pressure and DRPPT were not associated with reaching an endpoint. The small number of observed events precluded building a predictive model to identify high risk populations; given the low event rate, the study was underpowered to investigate prophylactic effects within subgroups.

Three control eyes versus one LPI-treated eye developed an acute attack after pupil dilation (one case was bilateral); when excluding these subjects, the HR ratio remained similar between the two groups (HR 0.54, 95%CI: 0.31-0.97, *p*=0.038). Subgroup analysis on each component endpoint demonstrated similar results, with 3 (0.66/1000 EY) LPI-treated eyes and 5 (1.11/1000 EY) control eyes developing IOP elevation on two repeated visits, 15 (3.31/1000 EY) LPI-treated eyes and 30 (6.64/1000EY) control eyes developing PAS of one clock hour or greater, 1 (0.22/1000EY) LPI-treated eye and 5 (1.11/1000EY) control eyes

experiencing an acute attack of PAC (1 LPI-treated eye and 3 control eyes after dilation, Table 2).

The study was initially designed to last three years but event rates were low and the investigators recognized that there would be insufficient power to draw any conclusions at three years. Prior to subjects completing 18 months of follow-up the protocol was amended with a revised 72-month endpoint. The Data Monitoring Committee suggested this change based on the low rate of endpoints and raised the possibility of increasing the sample size, extending follow up or both. Given the low event rates and our desire to complete the study in a timely fashion we elected to both increase the sample size and extend follow-up. The protocol was updated in the online registry. No difference in outcomes was seen in the larger study population at 3 years despite a small benefit of iridotomy at 6 years (Table S3, S4).

At each visit, the LPI-treated eyes and control eyes had similar presenting visual acuity and IOP measurements (Table 5). Angles were significantly wider after LPI than in untreated eyes, however, 49.4% of angles remained closed 2 weeks after LPI.[16] For LPI-treated eyes, the mean sum of all four Shaffer angle grades increased from 5.3±2.4 at baseline to 11.5±3.4 at 36 months, and then decreased to 9.6±3.4 at 72 months. For control eyes, the total angle width progressively decreased from 5.3±2.4 at baseline to 3.9± 3.1 at 72 months. No serious adverse events occurred during or immediately after LPI treatment (Table 6). Localized mild iris bleeding and corneal burns occurred in 28.9% (257/889) and 0.1% (1/889) after LPI,

respectively; 0.90% (8/889) needed repeat LPI treatment. Only six subjects (0.70%) had an IOP of 30mmHg or more one hour after LPI and all were given one drop of brimonidine 0.15% and 25 mg of methazolamide orally. The IOP of all 6 subjects returned to normal 2 hours after administration of medications and these subjects were discharged with a prescription of methazolamide 25mg TID for 2 days, at which time the IOP was rechecked and was normal in all cases. About 10% of participants reported subjective glare but the size and location of LPI were not associated with those symptoms.[17] At the end of 72 months, the endothelial cell densities and lens grading were similar between the two arms.

Discussion

Principal findings

The rate of developing any angle closure endpoint was much lower than expected in PACS eyes, less than 1% per year. Those undergoing LPI had a 47% reduction in the risk of developing PAC or an acute attack (HR 0.53, 95% CI 0.30–0.92; p=0.024). LPI itself was safe and no long-term adverse events were identified. The vast majority of endpoints were reached due to conversion from PACS to PAC, in particular on the development peripheral angle synechiae, a sign of mild damage from angle closure but is not associated with vision loss. These results argue that prophylactic LPI is of modest benefit over the timescale of our trial given the very low event rate observed and the limited harm of the vast majority of endpoints reached.

Comparison with other studies

The low rate of progression from PACS to PAC was unexpected. Few previous longitudinal studies have addressed the natural progression of PACS and PAC. In a 5-year Indian cohort study with 82 people with PACS and 37 people with PAC, 22% of those with PACS progressed to PAC and 28.5% with PAC progressed to PACG.[17,18] Among 129 individuals (94% Caucasian) with PACS equivalent, 19.4% developed a study endpoint during a mean 2.7-year follow-up in a clinical setting.[19] However, in a more recent community cohort of 485 Chinese individuals with PACS, only 4.1% progressed to PACG over six years of follow-up with a progressive reduction of anterior chamber depth occurring in 28% patients.[20] Another community-based study in Mongolia reported that 1.6% of those aged 50 years and older (with or without prophylactic LPI) eventually developed PACG in 6 years.[13] Our findings reveal even lower rates of incident disease, with only one in 20 untreated eyes developing PAC over this time. Of note, studies above used varying definitions of angle closure and did not report on standardization of gonioscopy across graders. We believe that our study results are likely more precise, as the sample enrolled was large with high retention rate, follow-up relatively long-term, and all study procedures were performed systematically at each visit. If we extrapolate our data to the population of China, among people aged 50 years and older (337 million), in whom 10% (33 million) have PACS, 260,000 people per year will develop PAC without LPI prophylaxis, and this number would be about half as large with iridotomies uniformly performed.

Clinical and policy implications

The results primarily suggest that the risk of developing PAC over 6 years is low but this needs to be understood in the context of the criteria we chose to define PACS and also how the patients were identified. In the present study, we defined PACS based on 6 clock hours or more of the anterior chamber angle having no visible trabecular meshwork on gonioscopy. This definition has been commonly used in most recent studies of angle closure,[21-23] but others have used 270 degree as the standard.[24-26] If we only selected those subjects with 270 degree or more of angle closure as the enrollment criterion, the incidence of PACS to PAC would have been effectively the same (4.81% versus 4.78%) over 6 years (Table S1). The incidence rate of progression was marginally higher for eyes with four quadrants of angle closure at baseline (5.40% over 6 years, Table S1). Therefore, the definition of PACS did not drive the finding of a low incidence rate of outcome events. We also did not observe a significant difference in results when choosing different PACS definitions [HR 0.54 (0.31-0.95), p=0.033 for 3 quadrants of angle closure ; HR 0.56 (0.32-0.98), p=0.044 for all 4 quadrants of angle closure, Table S1]. Another possible explanation for the low incidence rates could be the use of a community-based sample which likely selected those who were completely asymptomatic. Most researchers have enrolled clinic patients who may have already been experiencing subclinical angle-closure leading them to present, resulting in biased results relative to the community at large.

Researchers have attempted to identify other clinical features or examination methods besides gonioscopy, a traditional method on quantifying the degree of angle width, to

identify people at increased risk of developing PAC or PACG. Unfortunately, the longitudinal studies mentioned above did not identify any anatomical characteristics as good predictors for identifying individuals likely to develop glaucomatous damage from angle-closure. Furthermore, provocative tests also have not proven effective at predicting outcomes.[27] In our study, we screened all eligible participants with a dark room prone provocative test (DRPPT) and only one was excluded from the study prior to randomization for an IOP increase of 16 mmHg as a safety measure. We also found that the DRPPT did not help predict which eyes developed PAC although this analysis may have been hindered by the small number of incident cases.

LPI treated eyes had a 47% (HR 0.53, 95% CI 0.30–0.92 p=0.024) reduction in risk of progression to PAC compared to untreated eyes. Only one of the LPI-treated eyes developed an acute attack of angle closure (after protocol-indicated dilation) while five did so in control eyes (three after dilation). This suggests that there is a small and real risk of an acute attack and those at risk of developing an acute attack do benefit from LPI, but identifying this small subset at baseline is impossible. The overall annual risk reduction was 0.38%, and therefore the number needed to treat (NNT) was 44 to prevent one case of new primary angle closure disease over 6 years, the vast majority of which were not acute attacks. Assuming that these PAC cases have a 35% risk of developing sight loss from glaucoma over a further 5 years,[18] and assuming that prevention of sight loss would be the ultimate goal of prophylactic laser iridotomy, then the total number needed to treat (over approximately a decade) would be

around 126 people. Given the early nature of most incident PAC disease in our trial, the NNT would probably be higher. This may make LPI non-viable as a strategy for preventing loss of vision in socialized medicine systems or in health insurance systems, where other health interventions may be superior in terms of benefit:cost. That said, given the very low risk, we conclude that efforts to identify and treat with iridotomy on a population basis likely are not the best use of resources and healthcare systems would be more effective if they allocated resouces to identifying glaucoma earlier.

We recommend that people classified as PACS be told that the risk of future angle-closure glaucoma is low without LPI, but AAC can occur in rare cases and pupil dilation can result in AAC. Programmatic prevention of angle-closure requires a more pragmatic view, and based on the very low risk of developing PAC, community-based screening to identify PACS and perform LPI is not recommended.

Strengths and limitations

One of the major strengths of the current study is the fact that LPI was performed in only one eye, so all other individual-level confounders were controlled for since each participant acted as his or her own control. Based on previous results, we had planned on a 36 month study, but extended it to six years due to the low number of eyes converting to PAC. Additional strengths include low dropout, masked allocation, objective assessment of various parameters, long-term follow-up, and testing in an ethnic group with high risk of PACG. This trial also has limitations. First, due to the nature of the LPI procedure, it was not possible to

mask the participants and outcome examiners, which could have introduced observational bias. Since PAS was a primary endpoint, we did not use ASOCT as that likely would have missed PAS. Second, gonioscopy is partially subjective and it is possible that variability in gonioscopy grading may have led to non-differential misclassification which would have reduced our ability to detect a real difference if one existed. Finally, the findings from this study are only directly applicable to Chinese (i.e. high risk) subjects 50 years of age and older with PACS. Other populations may have a different response to iridotomy and additional studies are required.

Conclusions

In summary, incident disease occurred very rarely, and when it did, appeared relatively benign in nature although the prophylactic benefit of LPI was statistically significant. We estimate 44 people need to be treated to prevent one case of early disease over the subsequent six years, with no impact on visual function. Given these findings, we recommend against the widespread practice of performing LPI in PACS based on current definition. This will likely save considerable time and money, and avoid unnecessary medical interventions. In view of a recent trial showing superiority of phacoemulsification lens extraction over LPI in late stage PAC, and PACG,[28] consideration should be given to focusing resources on identifying these potentially blinding forms of angle-closure, and delivering more intensive treatment in a smaller number of patients who are at higher risk of loss of vision.

Footnotes:

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Ethical approval:

The protocol was approved by the Zhongshan Ophthalmic Center Medical Ethical Committee, China (November 2002 and [2007] No.12), Ethical Review Board of London School of Hygiene and Tropical Medicine, UK (17/03/2008, ref: 5267, 05/03/2011, ref: A240 5267), and Johns Hopkins University institutional review boards (NA_00015967, 4/7/2008)

Contributors:

MH, DSF, and PJF conceived and designed the trial. MH, PJF, DF and TA were the chief investigators and oversaw the trial throughout. YJ and SH were trial examiners. BM and DSC monitored the data and performed analyses and provided critical feedback to study design and activities. All authors contributed to the interpretation of data, drafting of the report, and decided on its content. All authors approved the final version.

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Figure legends

Figure 1 Flow diagram for the trial.

Figure 2 Kaplan-Meier plot of the study endpoint.