The Singapore Asymptomatic Narrow Angles Laser Iridotomy Study (ANA-LIS): 5 year results of a Randomized Controlled Trial.

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Abstract

Purpose: To examine the efficacy of laser peripheral iridotomy (LPI) in subjects diagnosed as primary angle closure suspects (PACS)

Design: Prospective, randomized controlled trial

Participants: This multi-center, randomized controlled trial (NCT00347178, Clinical trials.gov) enrolled 480 subjects over the age of 50 years from glaucoma clinics in Singapore with bilateral asymptomatic PACS (defined as having ≥2 quadrants of appositional angle closure on gonioscopy).

Methods: Each subject underwent prophylactic LPI in one randomly selected eye, while the fellow eye served as control. Subjects were followed up yearly for 5 years.

Main Outcome Measures: The primary outcome measure was development of primary angle closure (PAC, defined as presence of peripheral anterior synechiae, and/or intraocular pressure>21 mmHg or acute angle closure [AAC]) or PACG over 5 years.

Results: Of the 480 randomized subjects, the majority were Chinese (92.7%) and female (75.8%) with mean age of 62.8±6.9 years. LPI-treated eyes reached endpoint less frequently after five years (24, 5.0%, incidence rate [IR]=11.65 per 1000 eye-years) compared to control eyes (45, 9.4%, IR=21.84 per 1000 eye-years, p=0.001). The adjusted hazards ratio (HR) for progression to PAC was 0.55 (95%CI: 0.37-0.83, p=0.004) in LPI-treated eyes compared to control eyes. Older subjects (per year, HR=1.06, 95%CI: 1.03-1.10, p<0.001) and higher baseline IOP (per mm Hg, HR=1.35, 95%CI: 1.22-1.50, p<0.0001) were more likely to reach an endpoint. The number needed to treat in order to prevent an endpoint was 22 (95%CI: 12.8-57.5).

Conclusions: In subjects with bilateral asymptomatic PACS, eyes that underwent prophylactic LPI had significantly fewer endpoints compared to control eyes over 5 years. However, the overall incidence of PAC or PACG was low.

Key words: primary angle closure suspect, prophylaxis, iridotomy, clinical trial

Precis

Untreated primary angle closure suspects have a low likelihood of progression to glaucoma. Performing a laser iridotomy reduced the likelihood of progression by half.

Glaucoma is the leading cause of irreversible blindness worldwide with almost 70 million afflicted.[1] With the rapid increase in the elderly population worldwide, the prevalence of glaucoma is expected to reach 111.8 million by 2040. This has important public health implications for a condition in which visual loss, once established, cannot be reversed. Glaucoma is classified according to the configuration of the angle (the part of the eye between the cornea and iris mainly responsible for drainage of aqueous humor) into primary open angle (POAG) and primary angle-closure glaucoma (PACG). PACG causes a great amount of visual loss in Asia,[3-4] especially in populations of Chinese and Mongoloid descent,[5-7] and is nearly twice as likely to cause blindness compared to POAG.[1-4]

Eyes having anatomically narrow angles with appositional closure but without any other abnormality are termed primary angle-closure suspects (PACS). Primary angle-closure (PAC) is present when a person has narrow angles along with evidence of a secondary effect which includes the formation of peripheral anterior synechiae (PAS) and/or raised intraocular pressure (IOP). There is no glaucomatous optic neuropathy (GON) in PAC. Finally, PACG is present when there is a narrow angle along with GON. The natural history and clinical course of PACS is not well established with reports of progression to PAC ranging from 19.4% to 33% over 5 years.[2-9] Most of the data are limited by studies being mainly retrospective with small sample sizes.

Prophylactic laser peripheral iridotomy (LPI) is frequently performed to prevent PACG, but evidence supporting this is weak.[5-9] While LPI is easy to perform and low-risk, it is not known if LPI is cost effective or warranted for all cases of PACS as many eyes would probably never develop disease, let alone visual disability. Certainly, in countries like China and India with populations exceeding one billion, mass laser treatment for large at-risk populations is an expensive proposition, requiring strong evidence of cost effectiveness. Furthermore, while LPI appears relatively safe, even rare adverse consequences of the procedure such as cornea damage, cataract progression[11,12] and visual symptoms[13-16] could overwhelm any benefit if LPI were used in all PACS cases.

Recently, the Zhongshan Angle Closure Prevention (ZAP) Trial found a low incidence of PAC (defined as development of PAS, elevated IOP or acute attacks) amongst individuals with PACS identified through community screening in Guangzhou, China.[10] Of the 889 patients randomized, only 19 lasered and 36 control eyes developed these endpoints over six years of follow-up. The reported incidence was lower than had been anticipated based on previous retrospective and clinic-based studies. We report on a similar randomized controlled

trial (RCT) of prophylactic LPI for PACS in patients recruited from eye clinics in Singapore to compare LPI versus no treatment in preventing the development of PAC/PACG over 5 years.

Methods

Study Design

The Singapore Asymptomatic Narrow Angles Laser Iridotomy Study (ANA-LIS) was an open-label, paired-eye, RCT of prophylactic LPI versus no treatment in PACS (NCT00347178, Clinical trials.gov). Subjects were recruited from 5 Singapore eye centers, and were randomized to have one eye treated with LPI, and the other eye untreated to serve as control. Besides a baseline visit and a safety visit one week post-LPI, subjects had follow-up visits at 12, 24, 36, 48 and 60 months. Written informed consent was obtained from all subjects and the trial was approved by the ethics committees of the respective institution review boards representing the centers in Singapore. A separate data and safety monitoring center (Singapore Clinical Research Institute, SCRI) monitored the safety of the trial, data entry and analysis.

Participants

Patients aged 50 years or above with bilateral PACS (defined as having ≥2 quadrants of appositional angle closure with non-visibility of the pigmented posterior trabecular meshwork [PTM] on non-indentation gonioscopy), and capable of giving informed consent were eligible for enrolment. The following exclusion criteria applied: IOP>21 mm Hg at any previous visit, a post-pupil dilation IOP spike greater than 15 mm Hg, presence of PAS (defined as at least half-clock hour of iris adherent to posterior trabecular meshwork in any quadrant on indentation gonioscopy), GON (defined below), secondary angle closure, prior incisional or laser surgery or penetrating eye injury, corneal disorders such as corneal endothelial dystrophy or corneal opacity preventing LPI, prior episode of acute angle closure (AAC, defined below), significant cataract requiring surgery, best-corrected visual acuity less than 20/40, use of contact lens, chronic use of topical or systemic steroids, retinal diseases requiring regular pupil dilatation, any other disease likely to cause visual field loss, or severe health problems resulting in a life expectancy of less than 1 year precluding follow-up.

Randomization and masking

After verifying eligibility and obtaining written informed consent, each subject was randomized by delegated site personnel with a password-secured account through the SCRI randomization website and a trial number assigned. One eye was randomized to undergo LPI, while the other eye remained untreated. Treatment allocation was not masked due to the nature of the intervention.

Procedures

A questionnaire was administered to collect relevant demographic information, history of past ocular and medical conditions including diabetes mellitus and hypertension, family history of glaucoma and current medications. At baseline and annual follow-up visits, the following assessments were performed: best corrected visual acuity (BCVA) at 4 meters using the Early Treatment Diabetic Retinopathy Study (ETDRS) logarithm of the minimal angle of resolution (logMAR) visual acuity (Lighthouse International, NY, USA), slit lamp examination (model BQ-900; Haag-Streit, Koniz, Switzerland), Goldmann applanation IOP measurement (see details below) pre and post-pupil dilation, static and dynamic gonioscopy using both 2-mirror Goldmann-type gonioscope and Sussman (Ocular instruments Inc., Bellevue, WA) gonio lens, LOCS III cataract grading, optic disc examination using 78 D lens with a slit lamp graticule, visual field testing using Humphrey Visual Field Analyzer II (Swedish Interactive Testing Algorithm 24-2, Carl Zeiss Meditec, Dublin, USA), endothelial cell count by specular microscopy, A-scan Ultrasound (Echo scan, Nidek Co Ltd), keratometry (Canon RK-5, Tokyo, Japan), central corneal thickness by ultrasound pachymeter (Advent, Mentor O&O, USA) and optic disc photos (Canon CR545NM, Tokyo, Japan). Limbal anterior chamber depth (ACD) was determined using the modified Van Herick technique[17], with the temporal peripheral anterior chamber examined under optical section at x16 magnification. Axial length (Axl), central ACD and lens thickness (LT) were measured using A-scan ultrasound. Standard deviation was fixed at 0.02 mm for quality control. The readings were repeated if the criteria were not met. Three IOP measurements were recorded for each eye at each visit and the median value recorded. Intra-class correlation coefficient was 0.9 for IOP measurement between observers. Gonioscopy was performed under standard dark illumination in all participants. A narrow beam of 1 mm in length was offset vertically for superior and inferior quadrants, horizontally for nasal and temporal quadrants. Modified Shaffer grading system[18] was used to grade the angle width from 0 to 4 and the sum of which was considered as the total angle width on gonioscopy. If the posterior trabecular meshwork was not visible in primary position, the

angle was considered as “closed.” Examiners were trained using a standardized gonioscopy technique, and the agreement for detecting 180 degrees of appositional angle closure was found to be 0.82 (kappa) between them. Dynamic indentation gonioscopy was used to determine the presence of PAS. Any presence of PAS was confirmed by two independent glaucoma fellowship-trained observers on the same day. VCDR was measured using a graticule attached to the slit lamp. The intraclass correlation coefficient between examiners for VCDR assessment was >0.8. The visual field test was repeated if the test reliability was not satisfactory (fixation loss >20%; false positive>33%; and/or false negative>33%) or if there was a glaucomatous visual field defect.

Intervention

LPI was performed by sequential argon and YAG laser within a week of the baseline visit. One drop of brimonidine 0.15% was instilled in the intervention eye 30-45 minutes prior to laser in order to reduce IOP spikes. Subjects were treated in the superior (from 10 to 2 o’clock) peripheral third of the iris, where the iris appeared thinnest (preferably in a crypt) with the argon laser until a partial thickness hole was created. The YAG laser was then used to complete the procedure. The argon laser settings were 500mW-1000mW with a spot size of 50 µm for duration of 0.05-0.1 seconds. The energy level was adjusted according to the tissue response. The YAG laser (Visulas YAG III, Carl Zeiss Meditec, Dublin, CA, USA) was initially set at 2–5 mJ. All iridotomies were performed using an Abraham lens (Ocular Instruments, Bellevue, WA) after application of a coupling agent. The size of the iridotomy was at least 200 µm. The IOP was re-tested one hour after completion of LPI. Subjects who had an increase in IOP of >8 mmHg at one hour were given a drop of brimonidine and a tablet of acetazolamide 250 mg (if not contraindicated) and IOP re-checked one hour later. If IOP had not risen over the second hour, the patient was discharged and examined the following morning. If IOP had risen further, the patient was referred to a glaucomatologist for further management. After LPI, all subjects received betamethasone 0.1% drops 3-hourly for the first 24 hours followed by four times a day for one week.

Outcomes

The primary outcome measure was the development of:

1. PAC defined as the presence of: (a) ≥ half-clock hour of PAS formation, or (b) IOP >21 mm Hg verified on two separate days, or (c) development of an AAC event. AAC was defined by the following criteria: i) presence of at least 2 of the following symptoms: ocular or periocular pain, nausea and/or vomiting, an antecedent history of intermittent blurring of vision with haloes; ii) IOP≥30 mm Hg and iii) presence of at least 3 of the following signs: conjunctival injection, corneal epithelial edema, mid-dilated unreactive pupil, glaucomflecken and shallow anterior chamber; OR
2. PACG defined as the presence of GON with visual field loss compatible with glaucoma. GON was defined as loss of neuroretinal rim (notch or erosion) with a vertical cup-disc ratio of >0.7 and/or nerve fibre layer defect attributable to glaucoma.

During follow-up, a subject presenting with a history of at least 2 symptoms (headache, eye pain, haloes, nausea/vomiting and blurred vision) and eye redness but in the absence of measured raised IOP was considered as 'presumed symptomatic PACS'. These subjects were assumed to have intermittent AAC with undocumented rise in IOP in the absence of other ocular or systemic causes. For safety reasons in such cases, untreated eyes underwent LPI based on consensus between treating physician and study team.

Termination of follow-up (Censored data)

Fellow eyes underwent LPI during follow up if either eye reached the primary end point. Subjects also exited the study if there was need for cataract surgery, development of retinal diseases (such as retinal vein occlusion, moderate or severe diabetic retinopathy, macular conditions requiring surgical intervention like epiretinal membrane or macular hole) or development of uveitis that needed chronic treatment. All these above conditions were considered as requisites for termination of follow-up and were defined as censored data.

Statistical analysis

Analysis of baseline and efficacy data were on an intention-to-treat basis where eyes were classified as control and LPI-treated as per randomization. The number of eyes that developed PAC and/or PACG were summarized with its timing and incidence rate by treatment arm. The main analysis of the primary outcomes was performed using a Cox regression model with the cumulative incidence approach for competing risks and with a robust sandwich estimate for within-subject correlation. The regression model was adjusted for age, sex, diabetes, and baseline ocular parameters. As supportive analysis, the development of the primary outcome in relation to LPI was tested by the McNemar test, together with the 95% confidence interval (CI) for the difference in proportion between the LPI-treated and control eyes using Newcombe's method based on score intervals with continuity correction. The corresponding number needed to treat (NNT) was determined. The same analyses were applied to other efficacy outcome measures. The number and proportion of subjects with adverse events (AE) and the number of events were collected and summarized. For eye-specific AEs, the number of eyes that experienced the events were counted and compared between LPI-treated and control eyes. Statistical analysis was performed with SAS® version 9.4.

For sample size calculation, the 5-year incidence of PAC/PACG in people aged 50 years and older without treatment was estimated to be 5.75% based on the data from Seah et al, 1997.[19] Assuming LPI was effective in preventing development of PAC/PACG such that the relative risk was 25% between LPI and no treatment, the required number of subjects (i.e., paired of eyes) was 435 for 90% power and two-sided 5% type I error. This was increased to 480 subjects to allow for a 10% drop-out. This calculation ignored the within-subject correlation between eyes. Hence the actual power was greater than 90% with the assumed parameters.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit.

Results

A total of 480 subjects were randomized into the study between Jan 2005 and Aug 2010 from a total 1084 subjects screened for eligibility. Reasons for screen failures (n=604) are summarized in **Figure 1**, with the main reason being 'declined to participate' (n=333). Of the randomized subjects, 3 did not receive LPI due to patient refusal. Of the remaining subjects who received LPI, 58 subjects (12%) either withdrew or were lost to follow up. The CONSORT flowchart of the study is shown in **Figure 1**.

The 480 randomized subjects had a mean age of 62.8 years (standard deviation [SD] = 6.9) and the majority were female (75.8%), and of Chinese ethnicity (92.7%). Hypertension was common amongst the subjects (47.7%), and other less prevalent existing diseases at baseline were diabetes mellitus (14.6%) and ischemic heart disease (6.3%). The eye-specific baseline characteristics are summarized in **Table 1 and 1a**.

Main Outcome

At the end of 5 years of follow up, the number of eyes that reached one of the primary endpoints was significantly lower in LPI-treated eyes (24 [5.0%, 95%CI: 3.4%-7.3%]) than in control eyes (45 [9.4%, 95%CI: 7.1%-12.3%, p=0.001). The incidence rate for development of an endpoint was 11.65 per 1000 eye years in the LPI-treated eyes compared to 21.84 per 1000 eye years in control eyes (p=0.001). The estimated cumulative incidence and point-wise 95%CI for the primary outcome are provided in **Figure 2 and Table 2**. The overall unadjusted hazards ratio (HR) was **0.52** (95%CI: 0.35-0.78) for development of the primary outcome over 5 years in LPI-treated eyes compared to control eyes. The NNT benefit of prophylactic LPI for PAC and/or PACG was 22 patients to prevent a single endpoint in 1 patient over 5 years (NNT benefit: 21.2 [95% CI: 12.8-57.5]), with the NNT benefit being 26.2 (95% CI: 14.8 – 96.2) for PAC, and 103.1 (95% CI: 34.8 - inf) for PACG. Based on an observed incidence of 10.21% for PAC and/or PACG over 5 years in the control arm of this study, and a PACS prevalence of 6-10 % in the Singapore population aged 50 years and over, the population attributable risk percentage of PACS for PAC and/or PACG was 38.3% to 50.8%.

The benefit of treatment was mainly mediated through a reduction in the development of PAS (LPI 1.3% over five years vs controls 4.9%, p<0.001, **Table 2**). Progression to PACG was uncommon in both groups (LPI 0.6% vs controls 1.5%, p=0.23). Even fewer eyes developed IOP>21 mmHg or AAC (LPI 0.2% vs control 0.4%, p=0.57). One of the treated eyes developed acute anterior uveitis with closure of LPI and subsequently developed AAC.

'Presumed symptomatic PACS' was diagnosed in 4 of the untreated eyes (not considered an endpoint, but they underwent early LPI and exited the study). Older subjects (per year, adjusted HR=1.06, 95%CI: 1.03-1.10, p<0.001) and those with higher baseline post dilatation IOP (per mm Hg, adjusted HR=1.35, 95%CI: 1.22-1.50) (**Table 4**) had a higher risk of developing the primary outcome in Cox regression analysis. Those with diabetes had nearly twice the risk, but this was not statistically significant (HR=1.88, 95%CI: 0.98 -3.63, p=0.06) The adjusted HR of developing PAC/PACG was 0.55 (95%CI: 0.37-0.83) between LPI-treated eyes and control eyes (after adjustment for demographics, diabetic status and ocular parameters, **Table 4**). Both best corrected distance and near visual acuity were comparable between treatment arms over 5 years (**Table 5**). LPI appeared to have a transitory impact on both pre- and post- dilatation IOP, resulting in a lower IOP compared to control eyes at the year 1 visit. Grading of mean angle width on gonioscopy was wider in the LPI treated eyes than in the control eyes at all follow-up visits from week 1 to year 5. Findings on limbal anterior chamber depth grade were similar to angle width.

Safety

Nine deaths were reported in the study, of which 4 were due to cancer, 2 to heart disease, 1 suicide, and 2 of unknown cause. There were 27 serious adverse events (SAEs) reported, of which 8 were eye-specific (5 in LPI-treated eyes, 3 in control eyes) consisting of 3 documented AAC (1 in LPI-treated eye and 2 in control eyes), 1 branch retinal artery occlusion, 1 rhegmatogenous retinal detachment, 1 posterior chorioretinitis, 1 acute anterior uveitis, and 1 macular branch retinal vein occlusion. Two subjects who had AAC (one in LPI-treated eye and the other in control eye) had 6/6 BCVA before the AAC episode and required standard management of AAC followed by LPI to recover vision completely. One subject who had AAC in the control eye (at 2 ½ years after enrollment) underwent cataract surgery, and later required penetrating keratoplasty but final vision was poor (Counting fingers). All SAEs and deaths were considered not related to LPI except AAC. None of the subjects in the LPI group had an IOP ≥30 mm Hg immediately after LPI. Specular microscopy at 60 months showed no difference in hexagonality of cells but a higher mean cell area in the LPI group compared to baseline (**Table 6**) and a greater cell density in control eyes compared to LPI-treated eyes at 60 months. Eye-specific AEs such as eye pain, dry eyes, redness of eyes and ocular discomfort were rare in both LPI-treated eyes and control eyes – each occurring in less than 5% of eyes (**Table 6**). These were overall more common in LPI-treated eyes (22%) than in control eyes (14.5%, p<0.001). The majority of eye-specific AEs

were of mild (68.6%) or moderate (26.7%) severity; treatment was provided to 64.3% of the eyes with AEs mostly with tear supplements.

Discussion

The incidence of reaching an endpoint in untreated PACS eyes was about twice that of eyes undergoing prophylactic LPI; most of this difference attributable to a nearly three-fold higher rate of developing PAS. The overall incidence of any endpoint after five years was low, even in the control group. This 45% reduction in risk, mostly from preventing the development of PAS, mirrors the findings from the only other randomized controlled trial of the treatment of PACS, the ZAP trial. With the exception of two eyes that developed AAC in the control arm (and one in the treated arm), all other endpoints did not have an immediate threat to vision. Only 10 eyes developed PACG, with no significant difference between the two treatment arms. Older age and higher baseline post dilatation IOP increased the risk of developing an endpoint.

Previous research on PACS has largely been composed of retrospective chart analyses, but some studies have prospectively assessed subjects.[20,21] One such study conducted at many locations in the United States[3] followed a mostly European-derived cohort with PACS and reported that nearly one in five untreated patients developed PAC over 5 years, nearly twice the rate of the untreated eyes in the present study. One practice in South India reviewed charts prospectively and reported that 22% of untreated PACS progressed to PAC,[22] and 28.5% of untreated PAC progressed to PACG over 5 years.[23] Similarly, a retrospective chart review from Vietnam reported high rates of transitioning from PACS to PAC despite the presence of an LPI; 22.2% over about ten years.[24] While not the same as the current randomized population, the incidence of PACG among high-risk individuals in Mongolia (defined as eyes having ACD<2.53 mm) at 6 years was 1.61% (95%CI 1.11%-2.25%), which was similar to our study.[25]

The lower rate of developing PAC from PACS in the present study is likely explained by several factors. First, the definitions used to define angle closure varied across studies. Second, retrospective chart reviews lacked standardized methods and "progression" could in part be explained by variation in examination technique. Third, the use of different gonioscopy lenses could have resulted in differences in classification; subjects in previous studies might have had PAS but were not identified if indentation gonioscopy was not performed. This would have led to underestimation of the incidence of PAC. Fourth, there may be real differences in the populations studied; Vietnamese and Indian angle closure may behave differently. Finally,

it is possible that the low progression rate seen in our study could be due to earlier stage of disease at baseline. However, more than 90% of the eligible participants had 270° or more of appositional closure at baseline.

The best direct comparison to the current study is the ZAP trial[10] which also mainly focused on a southern Chinese population. The ZAP trial reported a lower incidence of reaching endpoints over 6 years, 4.2 per 1000 eye-years in treated eyes compared to 11.7 per 1000 treated eye-years in the present study. Similarly, the ZAP trial reported 8.0 per 1000 eye-years in control eyes whereas we found 21.8 per 1,000 eye-years. Given the lower incidence of endpoints in the ZAP trial, the NNT was substantially higher in that study, 126, as opposed to 22 in the present study. The lower overall incidence of endpoints in the ZAP trial may be due to the different recruitment strategies employed; the ZAP trial enrolled from the community while we recruited patients from eye clinics. Patients who make it to care may be more likely to get worse owing to unmeasured factors. Subjects in the ZAP trial in fact had wider total angle width at baseline than those in the present study (5.3 vs 2.5). We also included non-Chinese participants who may have had higher risk. Surprisingly, eyes in the present study had longer Axl and ACD and shorter LT than subjects in the ZAP trial, which would seem to increase the likelihood of developing endpoints. That said, more cases of early cataract (based on LOCS grading) and more eyes with 360° of appositional closure were present in our cohort which may have predisposed to the development of endpoints. Another important possible explanation for the differences in incidence rates is the different IOP cutoffs used in the two studies. The ZAP trial used an IOP cut-off of ≥ 24 mmHg while we used >21 mmHg. Of note, only 7.2% of endpoints in our study were due to IOP which does not fully explain the differences seen.

Both our study and the ZAP trial found LPI to be safe for PACS. Development of AAC was the most significant concern in PACS eyes without LPI; however, the incidence was low overall (1 in LPI-treated eye and 2 in control eyes) in our trial. One case of AAC occurred in a treated eye due to blockage of LPI after acute anterior uveitis. A few patients complained of intermittent eye pain, headache and redness and were considered to have ‘presumed symptomatic PACS.’ Due to safety concerns, the managing physician was allowed to perform LPI in such cases, and this could have reduced the incidence of acute attacks or other endpoints in these patients which means our estimate of the incidence rate may be an underestimate of the true rate. Retinal events occurred equally in treated and untreated eyes. The ZAP trial reported no significant change in corneal endothelial cell density at 72 months between the two

groups. In contrast, we found, lesser cell density and larger cell area at 60 months, suggesting some damage to the endothelium from LPI. In the ZAP study, the logMAR VA at the endpoint was 0.29 which is about 20/40, a doubling of the visual angle and a level at which cataract surgery may be contemplated. In contrast, our subjects in both groups maintained best corrected distance visual acuities from baseline to 5 years. This could be due to early cataract staging at baseline and/or subjective refraction performed at 5 years.

Apart from older age, an established risk factor for glaucoma progression, higher post dilatation IOP was identified as a predictor of developing an endpoint in this study. Diabetes mellitus was also observed as a borderline risk factor. Diabetes mellitus is known to affect the autonomic nervous system, and thus can influence iris convexity, and pupil size, which may possibly increase the risk of development of PAC. A literature search revealed that Thomas et al[12] did not identify any predictors for progression of angle closure in their study of PACS, while Ramani et al[27] identified anterior chamber angle width (using ultrasound biomicroscopy) as a predictor for progression in untreated South Indian eyes over 3 years. Among 469 Canadian subjects with treated PACS eyes, older age and presence of PAS were found to be associated with progression over 8.5 years.[28]

Both the present study and the ZAP trial found that the vast majority of endpoints reached were due to development of PAS. While PAS may be of concern and could indicate future difficulty with IOP control, the fact remains that no differences were seen in the treated and control eyes developing an IOP>21 in the present study, and no differences were seen in the development of PACG. Due to the limited beneficial effect of LPI, the ZAP trial authors did not recommend widespread use of LPI in asymptomatic PACS. The evidence from the current study also suggests a limited benefit for prophylactic LPI in asymptomatic PACS, as the NNT for benefit was 22, and almost all the benefit was for visually insignificant angle changes. There would be no benefit of treatment in either study if PAS had not been chosen as an endpoint. It is possible that the differences between the numbers between the studies could be attributable to either overdiagnosis of PAS in our study or under identification of PAS in the ZAP trial. While we acknowledge the need to identify a subset of PACS individuals who would most benefit from prophylactic LPI, the absence of a clear risk predictor in this study should further kindle debate on the need for LPI in all asymptomatic PACS, given the cost and possible post LPI management involved. However, health care systems with higher diabetes related eye complications, less monitoring opportunities and lesser cataract surgery rates may

have different recommendations, which need further evidence in order to guide the optimum management strategies.

Our study had several strengths. Using one eye for treatment and the contralateral eye as the control removes confounding for all but ocular factors and these almost certainly are highly similar between the two eyes of a single individual. The sample size was large with good follow-up rate over 5 years. The sample represents asymptomatic PACS subjects presenting at eye clinics, which is a pragmatic and common clinical situation in Asia. A separate safety and data monitoring system provided unbiased management of the study and data. However, our study also had some limitations. Not all patients completed the 5 years of follow-up, with many dropping out of the study due to cataract surgery. Other environments where cataract surgery is not as readily available may have higher incidence of endpoints as some of these individuals likely would have gone on to develop endpoints. Finally, it was impossible to mask the intervention in this study, and this may have led to measurement bias for vision, IOP and other ocular parameters. However, we minimized this potential by including standard measurement techniques and repeated measurements especially for endpoints.

In summary, we found that untreated PACS eyes had twice the risk of developing endpoints, mostly PAS, over 5 years compared to eyes that underwent prophylactic LPI. The overall progression rate was low. Older age and higher post dilatation IOP were associated with an increased risk of developing an endpoint. Our findings confirm much of what was reported in the ZAP trial, further supporting the recommendation that observation without LPI is a reasonable option for PACS.

Contributors:

The study design was conceived by TA , DF and PJF. Trial management and oversight was done by TA, HTW, PTKC and MB. Patient recruitment and data collection was done MB, RSK, HTW,PTKC,RL,AN,SAP and TA. Statistical analysis was done by QSL and Singapore Clinical Research Institute, Singapore. MB and TA did initial manuscript preparation, and all authors reviewed and approved the final manuscript.

Declaration of interests

We declare no conflict of interests.

Data sharing

All data requests should be submitted to the corresponding author (TA) for consideration. Access to anonymised data may be granted for non-commercial research at the discretion of the Chief Investigator (TA).

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References

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014; **121**: 2081-90.
2. Alsagoff Z, Aung T, Ang LP, Chew PT. Long-term clinical course of primary angle-closure glaucoma in an Asian population. Ophthalmology.2000; **107**: 2300-4.
3. Wilensky JT, Kaufman PL, Frohlichstein D, et al. Follow-up of angle-closure glaucoma suspects. Am J Ophthalmol 1993; **115**: 338-346.
4. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol* 2002; **86**: 238-42.
5. Sawada A, Sakuma T, Yamamoto T, Kitazawa Y. Appositional angle closure in eyes with narrow angles: comparison between the fellow eyes of acute angle-closure glaucoma and normotensive cases. *J Glaucoma* 1997; **6**: 288-92.
6. Friedman DS, Gazzard G, Foster P,et al. Ultrasonographic biomicroscopy, Scheimpflug photography, and novel provocative tests in contralateral eyes of Chinese patients initially seen with acute angle closure. *Arch Ophthalmol*2003; **121**: 633-42.
7. Snow JT. Value of prophylactic peripheral iridectomy on the second eye in angle-closure glaucoma. *Trans Ophthalmol Soc UK* 1977; **97**: 189-91.
8. Fleck BW, Wright E, Fairley EA. A randomized prospective comparison of operative peripheral iridectomy and Nd: YAG laser iridotomy treatment of acute angle closure glaucoma: 3 year visual acuity and intraocular pressure control outcome. *Br J Ophthalmol* 1997; **81**: 884-8.
9. Nolan WP, Foster PJ, Devereux JG, et al. YAG laser iridotomy treatment for primary angle-closure in East Asian eyes. *Br J Ophthalmol*2000; **84**: 1255-9.
10. He M, Jiang Y, Huang S et al. Laser peripheral iridotomy for the prevention of angle closure: a single-centre, randomized controlled trial. *Lancet*2019;**393**(10181):1609-18.
11. Caronia RM, Liebmann JM, Stegman Z, Sokol J, Ritch R. Increase in iris-lens contact after laser iridotomy for pupillary block angle closure. *Am J Ophthalmol* 1996; **122:** 53-7.

12. Vijaya L, Asokan R, Panday M, George R. Is prophylactic laser peripheral iridotomy for primary angle closure suspects a risk factor for cataract progression? The Chennai Eye Disease Incidence Study. *Br J Ophthalmol* 2017;**101**:665-70.
13. Spaeth GL, Idowu O, Seligsohn A, et al. The effects of iridotomy size and position on symptoms following laser peripheral iridotomy. J Glaucoma 2005; **14:** 364-7.
14. Congdon N, Yan X, Friedman DS, et al. Visual symptoms and retinal straylight after laser peripheral iridotomy: the Zhongshan Angle-Closure Prevention Trial. *Ophthalmology* 2012; **119**: 1375-82.
15. Vera V, Naqi A, Belovay GW, Varma DK, Ahmed II. Dysphotopsia after temporal versus superior laser peripheral iridotomy: a prospective randomized paired eye trial. *Am J Ophthalmol*2014; **157**: 929-35.
16. Srinivasan K, Zebardast N, Krishnamurthy P, et al. Comparison of new visual disturbances after superior versus nasal/temporal laser peripheral iridotomy: A prospective randomized trial. *Ophthalmology* 2018;**125**(3):345-51.
17. Foster PJ, Devereux JG, Alsbirk PH, et al. Detection of gonioscopically occludable angles and primary angle closure glaucoma by estimation of limbal chamber depth in Asians: modified grading scheme. *Br J Ophthalmol*2000;**84**:186–192.
18. South East Asia Glaucoma Interest Group. Asia Pacific Glaucoma Guidelines. 2nd Edition. 2008; Appendix 6B:80
19. Seah SK, Foster PJ, Chew PT, et al. Incidence of acute primary angle-closure glaucoma in Singapore. An island wide survey. *Arch Ophthalmol* 1997;**115**:1436-40
20. Choi JS, Kim YY. Progression of peripheral anterior synechiae after laser iridotomy. *Am J Ophthalmol*2005; **140**: 1125-7.
21. Alsbirk PH. Anatomical risk factors in primary angle-closure glaucoma. A ten year follow up survey based on limbal and axial anterior chamber depths in a high risk population. *Int Ophthalmol* 1992; **16**: 265e72.
22. Thomas R, George R, Parikh R, et al. Five year risk of progression of primary angle closure suspects to primary angle closure: a population based study. *Br J Ophthalmol* 2003; **87**: 450-4.
23. Thomas R, Parikh R, Muliyil J, et al. Five-year risk of progression of primary angle closure to primary angle closure glaucoma: a population-based study. *Acta Ophthalmol Scand* 2003; **81:** 480-5.

24. Peng PH, Nguyen H, Lin HS, Nguyen N, Lin S. Long-term outcomes of laser iridotomy in Vietnamese patients with primary angle closure. *Br J Ophthalmol* 2011; **95:** 1207-11.
25. Yip JL, Foster PJ, Uranchimeg D, et al. Randomised controlled trial of screening and prophylactic treatment to prevent primary angle closure glaucoma. *Br J Ophthalmol* 2010; **94**: 1472-7.
26. Jiang Y, Chang DS, Zhu H, et al. Longitudinal changes of angle configuration in primary angle-closure suspects: the zhongshan angle-closure prevention trial. *Ophthalmology* 2014; **121**: 1699-705.
27. Ramani KK, Mani B, George RJ, et al. Follow-up of primary angle closure suspects after laser peripheral iridotomy using ultrasound biomicroscopy and A-scan biometry for a period of 2 years. *J Glaucoma*2009;**18**: 521-7.
28. Blondeau P, Jaworski L, Turcotte PC. Follow-up of angle closure glaucoma suspects after laser iridotomy in Caucasians with normal intraocular pressure at diagnosis. *Can J Ophthalmol* 2011; **46**: 247–53.