Title: Acute Angle Closure Attacks Are Uncommon in Primary Angle-Closure Suspects: The Zhongshan Angle Closure Prevention Trial

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Running Head: Pharmacologic Pupillary Dilation in PACS

Abbreviations: acute angle closure (AAC), primary angle-closure suspects (PACS), Zhongshan Angle Closure Prevention Trial (ZAP Trial), laser peripheral iridotomy (LPI), intraocular pressure (IOP), peripheral anterior synechiae (PAS), dark room prone provocative test (DRPPT).

Key Words: Angle closure, Mydriasis, Laser peripheral iridotomy, Glaucoma

Abstract

Purpose: Angle-closure glaucoma is a major cause of blindness worldwide that carries an excess risk of severe, bilateral visual impairment. A common concern among clinicians is precipitating acute angle closure (AAC) attacks by mydriasis. We evaluated the risk of AAC after pharmacologic dilation in Chinese individuals classified as bilateral primary angle-closure suspects (PACS).

Design: Randomized interventional controlled trial.

Participants: A total of 889 bilateral PACS aged between 50 and 70 years were identified through community screening in Guangzhou, China and enrolled in the study.

Methods: In the Zhongshan Angle Closure Prevention (ZAP) Trial, bilateral PACS were treated by laser peripheral iridotomy (LPI) in one randomly selected eye, with the fellow eye serving as an untreated control. Over 72 months of follow-up, participants had their pupils pharmacologically dilated six times with 5% phenylephrine and 0.5% tropicamide.

Main Outcome Measures: Incidence and risk of post-mydriasis AAC in LPI-treated and untreated control PACS eyes.

Results: One bilateral AAC attack occurred after mydriasis at the two-week post-LPI visit. No other AAC events occurred in LPI-treated eyes. In untreated eyes, four additional attacks occurred: two after dilation (one at 54- and one at 72-months follow-up) and two spontaneously. The risk of post-mydriasis AAC in untreated eyes was one attack in 1,587 dilations. The risk of spontaneous AAC in untreated eyes was 0.44 per 1000 eye-years (95% CI: 0.11-1.77 per 1000 eye-years).

Conclusions: The risk of an incident AAC attack in PACS eyes was extremely low, even in a higher-risk group with repeated pharmacologic pupillary dilation over six years of follow-up. Prophylactic LPI reduced this small but real risk.

Trial Registration: ISRCTN.com identifier: ISRCTN45213099.

Introduction

People with narrow anterior chamber angles of the eye are termed primary angle-closure suspects (PACS) and are believed to be at high risk of developing acute angle closure (AAC) attacks. AAC attacks are ophthalmic emergencies in which the trabecular meshwork is obstructed by the peripheral iris, resulting in a sudden increase in intraocular pressure (IOP) that may severely and irreversibly damage the optic nerve. PACS are common in much of Asia; nearly 10% of people over 50 years of age are PACS,[1] and there are nearly 30 million PACS in China alone.[2] Given the higher risk of developing AAC after pupillary dilation,[3] clinicians are usually hesitant to administer medications with mydriatic effect to patients without consulting ophthalmologists. This leads to difficulty in assessing optic nerve health and the condition of the retina through non-dilated small pupils. As a result, not routinely dilating patients' eyes to avoid AAC may inadvertently lead to the underdiagnosis of other ophthalmic diseases and conditions, potentially resulting in larger medical issues.

One of the main benefits of laser peripheral iridotomy (LPI) is the ability to prevent AAC attacks. Prior to the widespread use of lasers in ophthalmic practice, contralateral eyes of AAC patients that did not receive a prophylactic iridectomy had a nearly 50% incidence of AAC, which was reduced to less than 2% in a long-term case series. The single AAC event in the case series was attributed to an incomplete iridectomy.[4] Subsequent publications have shown that iridotomy is equally effective as iridectomy in controlling IOP,[5] and AAC patients are at especially high risk of an attack in the fellow eye if not treated prophylactically with LPI. One clinic-based study from the United States reported that 8 out of 129 subjects with angle closure or shallow anterior chambers developed AAC over a mean of 2.7 years of follow-up.[6]

Despite the common clinical practice of deferring mydriatic drugs in patients with narrow angles, population-based epidemiologic studies indicate low rates of AAC after

dilation. In the Baltimore Eye Survey, no AAC cases occurred in 4,870 dilations; however, 38 eyes were not dilated based on penlight exam.[7] Furthermore, two cases occurred in 6,679 dilations in the Rotterdam Study,[8] and only one case occurred in over 37,000 dilations as part of a national diabetic retinopathy screening in Ireland.[9] A fourth study estimated the annual incidence of AAC to be 2.2 cases per 100,000 in the whole population in Scotland and attributed nearly 20% of the study's overall reported cases to topical dilating drops.[3] That said, many of the participants who were dilated in these prior studies had wide, not narrow, anterior chamber angles. The risk of developing AAC after mydriasis in populations with much higher rates of PACS, such as the Chinese population, remains largely unknown.

We recently published the results of the Zhongshan Angle Closure Prevention (ZAP) Trial, which randomized one eye to LPI and left the fellow eye untreated in patients with bilateral PACS.[10] We report here on the risk of AAC in untreated eyes as well as the risk after dilation in these individuals.

Methods

The full study protocol and planned statistical analysis of the ZAP Trial have been published in detail[11] but are summarized here for reference. In brief, the ZAP Trial was a single-center, randomized interventional controlled trial conducted at the Zhongshan Ophthalmic Center Clinical Research Center. The trial was approved by the Ethical Review Board of Sun Yat-sen University, the Ethics Committee of Zhongshan Ophthalmic Center, and the Institutional Review Boards of Moorfields Eye Hospital (via the London School of Hygiene and Tropical Medicine) and Johns Hopkins Hospital. The International Standard Randomized Controlled Trial Number was issued on May 6, 2008 (ISRCTN45213099). The trial was performed in accordance with all tenets of the Declaration of Helsinki, and written informed consent was obtained from all participants before enrolling in the study. The trial was supervised by an

independent data monitoring and safety committee, an independent trial steering committee, and an independent advisory committee.

Individuals 50 to 70 years of age from an urban district in Guangzhou, China were invited to receive a screening examination to identify eligible subjects. A total of 889 participants with bilateral PACS were enrolled in the study. PACS was defined as ≥6 clock hours of angle circumference in which the posterior, usually pigmented, trabecular meshwork was not visible under non-indentation gonioscopy, in addition to IOP ≤21 mmHg, no peripheral anterior synechiae (PAS), and no glaucomatous optic neuropathy. Exclusion criteria included severe health problems resulting in a life expectancy of less than one year, prior intraocular surgery or penetrating eye injury, media opacity preventing LPI, best-corrected visual acuity worse than 20/40, or an IOP increase >15 mmHg after mydriasis or after a 15-minute dark room prone provocative test (DRPPT). Eligible subjects were allocated to receive LPI in one randomly selected eye while the fellow eye was left untreated using a pre-generated list of random numbers to perform randomization.

Interventions

LPI was performed by a trained ophthalmologist per a standard clinical protocol with the use of an Abraham lens (Ocular Instruments, Bellevue, WA, USA). Fifteen minutes after one drop of brimonidine 0.15% and pilocarpine 2% was administered in the intervention eye, 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.

Each subject underwent pupillary dilation at 2 weeks, 6 months, 18 months, 36 months, 54 months, and 72 months using 5% phenylephrine and 0.5% tropicamide. IOP was measured by Goldmann applanation tonometry one hour after mydriasis. All subjects were sent home with one tablet of methazolamide 25 mg to take that evening and were advised to return to the Clinical Research Center if AAC symptoms developed. An IOP elevation of >8 mmHg was considered to be a clinically significant rise. Therefore, if a subject's IOP increased by >8 mmHg after dilation, pilocarpine 2%, brimonidine 0.15%, and one tablet of methazolamide 25 mg were administered as a proactive safety measure. However, any subjects who experienced an IOP elevation of >15 mmHg in either eye after dilation were considered to have an excessively high risk of AAC and were excluded from participating in the remainder of the trial for their safety. This occurred in one subject who was subsequently removed from the study but was ultimately included in outcome reporting; it was later determined by the Data Monitoring and Oversight Committee that the subject had reached one of the trial's endpoints with a bilateral attack.

Outcome measures

An AAC attack was defined as the onset of two or more of the following signs and symptoms: (1) eye pain and blurred vision with halos, as well as possible nausea or vomiting; (2) elevated IOP; (3) red eye, swollen cornea, shallower anterior chamber depth, or mid-dilated unreactive pupil.[12] 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 1 mm narrow beam. Angle width was assessed under static gonioscopy using Shaffer's grading system, in which 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. Each angle measurement was then recorded based on five grading categories (Shaffer grades 0-4 correspond to 0, 10, 20, 30, and 40 degrees, respectively). Sometimes the iris was bowed forward making visualization of the angle challenging, and in many of these eyes, the angle was open. Therefore, we allowed slight tilting of the gonioprism towards the angle being examined. However, we did not allow for greater manipulation, as this could lead to compression opening the angle. If the trabecular meshwork was not visible using the single-mirror lens, a dynamic examination with a four-mirror gonioscope (Sussman Four Mirror Gonioscope, Ocular Instruments, Bellevue, WA, USA) was performed to determine if PAS were present. If iridotrabecular contact was reversible with compression gonioscopy (i.e. the angle could be opened, resulting in no PAS), the subject was considered to be a 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). Cataract was graded using the Lens Opacity Classification System III (LOCS III) with reference to standard photographs.

Statistical analysis

The incidence of AAC was determined based on the duration of follow-up for each individual. Each subject was dilated multiple times; therefore, the likelihood of AAC per dilation was determined based on the number of dilations an individual had undergone. We used Kaplan-Meier failure curves to display event rates and log-rank tests to test for equality of failure curves. Student's t-test was used to compare the mean of baseline ocular characteristics between eyes with and without AAC. All statistical analyses were conducted using Stata 14.2 (StataCorp LP, College Station, TX, USA). The significance level was set at 0.05 using a two-side test.

Results

Of 1,087 eligible participants identified as bilateral PACS, 889 (82%) enrolled in the trial and were followed for 72 months. The mean age was 59.3±5.0 years, and 737 participants (82.9%) were female. Mean follow-up was 61.1±20.2 months and 74.7% of subjects successfully completed the study. LPI was performed in 24 control eyes over the course of the study.

In total, five subjects developed AAC: there were one bilateral and four unilateral attacks. The bilateral attack occurred at the two-week visit after receiving dilation. The four unilateral AAC attacks occurred in untreated eyes: two occurred spontaneously prior to the 36- and 72-months visits, and the other two attacks occurred at the 54- and 72-months visits after mydriasis (Figure 1). The incidence of AAC in LPI-treated eyes was 0.22 per 1000 eye-years (95% CI: 0.31-1.57 eye-years) and 1.11 per 1000 eye-years (95% CI: 0.46-2.66 eye-years) in untreated eyes (p=0.100 with log-rank test). Among AAC attacks that occurred without mydriasis, there were no cases in the LPI-treated group, whereas there were two cases in the untreated group (incidence: 0.44 per 1000 eye-years, 95% CI: 0.11-1.77 per 1000 eye-years). Translating this into annual risk, the risk of an AAC attack was 1 in 2,273 PACS eyes, assuming an individual did not receive treatment and dilation. The risk of AAC after mydriasis in LPI-treated eyes was 1 in 4762 dilations, and 1 in 1,587 dilations in untreated eyes.

The IOP of all five AAC patients returned to normal after being treated with topical (timolol, brimonidine, brinzolamide, pilocarpine, and/or prednisolone acetate) and systemic (methazolamide, mannitol, and/or methyl-prednisolone) medications followed by LPI. Vision of all five patients improved without permanent vision loss, and none of them required further surgical intervention.

All five participants who developed AAC attacks were female with mean age 59.5 years (range: 53-69 years). These participants also all had four quadrants closed on gonioscopy at baseline (Table 1). Eyes that developed an AAC attack were more hyperopic (p=0.013) and had shallower anterior chambers (p=0.022) compared to eyes that did not experience AAC. However, there were no differences in IOP, response to DRPPT, and cataract grade at baseline between AAC eyes and non-AAC eyes.

Discussion

PACS identified through community-based screening were unlikely to develop AAC with or without LPI. This was true even when dilating subjects repeatedly over a mean follow-up of more than five years. The only case of AAC in LPI-treated eyes occurred after mydriasis, corroborating previous reports that the risk of AAC after LPI in individuals with narrow angles is almost zero. This single case occurred at the two-week visit, and it is possible that the participant's iris was still swollen or the iridotomy was not sufficiently patent to prevent an acute attack. Overall, our results suggest that it is generally safe to dilate patients after an iridotomy.

Eyes without an iridotomy did have a small but real risk of AAC with repeated mydriasis. Therefore, it is reasonable to consider LPI for people who require frequent dilation, such as patients with diabetes mellitus who must be monitored closely for sight-threatening diabetic retinopathy. However, the results of the current study provide reassurance to patients who are untreated but still need to be dilated owing to symptoms such as an acute floater, as well as to patients who may experience a mydriatic side effect from many drugs including antipsychotics, antidepressants, anti-histamines, anti-epileptic drugs, sympathomimetics, antiparkinsonian agents, and botulinum toxin.[13] The risk of such dilation is small in population-based studies of individuals who presumably have mostly open

angles,[3,6,8] and was also low in the present study in PACS individuals from a higher-risk Asian population.

The findings also support facilitating a more balanced discussion with patients about the need for LPI in individuals with angle closure. The rate of acute attack in individuals not being routinely dilated was less than one in 2,000 per year. However, acute attacks can be devastating with about 10-15% of patients presenting bilaterally,[4,14] and about 18% of eyes suffering severe vision loss from the attacks.[15] In a long-term visual outcomes study on AAC in a predominantly Chinese Asian cohort, almost half of all the participants were found to have glaucomatous optic neuropathy upon mean follow-up of six years post-attack. That said, nearly half of patients who experience AAC return to normal vision after being treated.[15] Other important considerations to weigh are the potential risks of the LPI procedure. Previous studies have reported that LPI carries some risks of glare and other bright artifacts of light,[16,17] blood-aqueous barrier breakdown and sustained IOP rise in rare cases, anterior chamber bleeding, and cataract progression.[18] Therefore, the decision whether to receive LPI should involve a discussion between clinicians and patients around the harms of LPI and the low possibility of developing AAC without the procedure.

Our study must be interpreted in light of the ZAP Trial's design. First, the study cohort was comprised entirely of Chinese subjects and therefore the results may not be fully generalizable to other racial and ethnic groups. Specifically, given that the Chinese population has one of the highest risks of angle closure,[19] the AAC risk after dilation could be even lower in other populations. Second, the study participants were identified in the community and may differ in AAC risk from patients who typically present to clinic; patients who present for an exam may already be experiencing symptoms and at higher risk of an attack. We also excluded one participant with an IOP elevation greater than 15 mmHg after a short DRPPT, and this individual may have been more likely to develop AAC. Furthermore,

it is important to consider the potential effects on our results of medications that were administered to subjects after pupillary dilation. We provided methazolamide, an oral carbonic anhydrase inhibitor, to all subjects who were dilated, as well as other therapies to subjects who experienced a clinically significant IOP rise of >8 mmHg after mydriasis. Although we considered these proactive steps as necessary to protect trial participants from unnecessary and avoidable harm, the medications may have lowered the rate of AAC events. Unfortunately, whether or not these actions did affect the number of acute attacks cannot be determined. Finally, we treated four subjects (0.45%) who developed IOP elevation above 30 mmHg after dilation with IOP-lowering medications,[20] which may have also contributed to reducing the incidence of AAC in our study.

In conclusion, the incidence of AAC after repeated pupillary dilation with 5% phenylephrine and 0.5% tropicamide in this higher-risk group of Chinese PACS was low over 72 months of follow-up. LPI provided a protective effect but did not completely eliminate the risk of developing AAC.

Figure 1: Kaplan-Meier Estimates of AAC Attacks by LPI-Treated Versus Control Eyes

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