Title: Cataract progression after Nd:YAG laser iridotomy in primary angle-closure suspect eyes

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Synopsis

This randomized controlled trial demonstrates that treatment of asymptomatic narrow angles with Nd:YAG laser peripheral iridotomy is unlikely to influence the rate of cataract development over six years of follow-up.

Abstract

Background/Aims: Prophylactic laser peripheral iridotomy (LPI) is performed in primary angle-closure suspect (PACS) eyes to prevent acute angle-closure attacks. However, accelerated cataractogenesis is a potential risk of the procedure that may result in decreased visual acuity. We aimed to assess the long-term impact of LPI on cataract formation in Chinese PACS.

Methods: In the Zhongshan Angle Closure Prevention Trial (ISRCTN45213099), eligible bilateral PACS participants received LPI in one randomly selected eye, while the fellow eye remained untreated. Cataract was graded using the Lens Opacity Classification System III, and progression was defined as an increase in grade by at least 2 units in any category or cataract surgery.

Results: In total, 889 participants were randomly assigned to LPI in one eye only (mean age 59±5 years, 83% female). At 72 months, treated eyes had slightly higher average nuclear grades (p<0.001). However, there were no differences between eyes for predefined cataract progression (cumulative probability at 72 months: 21.2% in LPI vs. 19.4% in control, p=0.401) or cataract surgery (1% for both). While LPI-treated eyes had a 10% higher risk of progression over six years [HR=1.10 (95% CI 0.88-1.36)], this was not statistically significant. Visual acuity at 72 months was similar in treated and untreated eyes (p=0.43).

Conclusion: Although lenses were graded on average as slightly more opaque in laser-treated eyes, prophylactic Nd:YAG LPI did not cause significant cataract progression. Our results suggest that LPI treatment of asymptomatic narrow angles does not increase the risk of developing clinically meaningful cataract worsening over time.

Key Messages

What is already known on this topic: Accelerated cataractogenesis has previously been raised as a potential complication of laser peripheral iridotomy (LPI) but is an ongoing debate in the existing literature.

What this study adds: This randomized controlled trial shows that LPI does not cause increased cataract progression and related decreases in visual acuity in primary angle-closure suspect (PACS) eyes. The study's results are strengthened by its use of fellow eyes as a control group, standardized lens grading, and a long-term follow-up period.

How this study might affect research, practice or policy: This study increases the safety profile of LPI and contributes to future therapeutic decision-making for asymptomatic PACS patients.

Introduction

People with narrow anterior chamber angles (termed primary angle-closure suspects, or PACS) are believed to be at risk of developing primary angle-closure glaucoma and therefore are frequently treated with laser peripheral iridotomy (LPI) as prophylaxis. LPI has been proven beneficial for preventing acute attacks in the contralateral eyes of individuals who have suffered a unilateral attack of acute angle closure.[1] While LPI appears relatively harmless, few long-term studies have been performed to examine adverse outcomes from the procedure. One theoretical risk of LPI is the more rapid development of cataract due to alterations in fluid dynamics and post-laser inflammation. LPI disrupts the natural flow of aqueous humor in the eye, which results in a significant increase in lens-iris contact.[2] Theoretically, this may predispose people to an increased rate of developing cataract since less aqueous is in contact with the lens epithelium. Several studies have attempted to investigate this issue; however, follow-up has been short, no lens grading system was used, and no acceptable control groups were studied.[3–6] Our study aimed to assess the impact of neodymium:yttrium-aluminum-garnet (Nd:YAG) LPI on cataract formation in PACS randomized to LPI in one eye only.

Methods

The Zhongshan Angle Closure Prevention (ZAP) Trial is a single-center, randomized controlled trial assessing whether Nd:YAG LPI is superior to observation for managing patients with bilateral PACS. The study was approved by the Institutional Review Boards at Sun Yat-sen University, Zhongshan Ophthalmic Center, Moorfields Eye Hospital, and Johns Hopkins University Hospital. All participants gave written informed consent for participation in the study, and the trial was conducted in accordance with all tenets of the Declaration of Helsinki. The

International Standard Randomized Controlled Trial Number (ISRCTN) was issued on May 6, 2008 (ISRCTN45213099) by the ISRCTN registry. The study protocol and methods have been published elsewhere in detail but are summarized here for reference.[7,8]

In brief, individuals aged between 50 and 70 years from an urban district in Guangzhou, China underwent a screening examination to determine eligibility, and participants identified as bilateral PACS were enrolled in the study. PACS was defined as ≥180 degrees of angle circumference in which the pigmented trabecular meshwork was not visible under non-indentation gonioscopy in the absence of elevated intraocular pressure (IOP), peripheral anterior synechiae, glaucomatous neuropathy, or evidence of prior acute attack. Potential participants with severe health problems precluding follow-up, prior intraocular surgery or penetrating eye injury, media opacity preventing LPI, best-corrected visual acuity (BCVA) worse than 20/40, or an IOP increase of >15 mmHg after dilation or after a 15-minute dark room prone provocative test were excluded.

Eligible participants received Nd:YAG LPI in only one randomly selected eye to control for individual-level confounders. To perform the randomization procedure, a number was assigned to each participant according to the sequential order of enrolling in the trial. The assigned number corresponded to a separate random number and its accompanying eye assignment in a list that was pre-generated at Wilmer Eye Institute (Baltimore, MD, USA). The random number was concealed in an envelope with the corresponding chronological number written on the outside and sent to Zhongshan Ophthalmic Center (Guangzhou, China). A masked research nurse opened the envelope preceding the LPI procedure.

Trained ophthalmologists performed the LPI using an Abraham lens (Ocular Instruments, Bellevue, WA, USA), per the standard clinical protocol. One drop of brimonidine 0.15% and pilocarpine 2% was administered prior to the procedure. After 15 minutes had passed, an Nd:YAG laser machine (Visulas YAG III, Carl Zeiss Meditec, Dublin, CA, USA) starting at an initial setting of 1.5 mJ was used to create a patent iridotomy of ≥200 μm in diameter. Participants received the LPI beneath the superior lid in an area where the iris appeared thinnest but preferably in a crypt. All treated participants were sent home on dexamethasone 0.1% eye drops hourly for 24 hours and then four times daily for one week following the procedure.

Follow-up visits occurred at 2 weeks, 6 months, 18 months, 36 months, 54 months, and 72 months after the LPI. 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, USA). BCVA after subjective refraction was measured for all participants by an optometrist. IOP was first measured by non-contact tonometry (Topcon CT-80A, Tokyo, Japan), and then Goldmann applanation tonometry was used to confirm IOP elevation in participants with IOP >24 mmHg in either eye. Gonioscopy was performed in a standardized fashion by glaucoma specialists after training.

All ZAP Trial participants underwent cataract grading using the Lens Opacity Classification System III (LOCS III) for nuclear color (NC), nuclear opalescence (NO), cortical, and posterior subcapsular cataract (PSC) at the slit lamp (BQ-900, Haag-Streit, Switzerland) after

pharmacologic dilation of the pupil.[9,10] LOCS III standard photographs, mounted on a illuminated box, were referred to for every lens opacity assessment during the evaluation.[10] The lens opacity assessment was performed independently at each follow-up visit without referring to the grading outcomes in the previous visits. Cataract grading was carried out by three trained graders (ophthalmologists) who underwent an initial period of standardization and additional training sessions. Progression was defined as change of ≥2 grades in any category or having cataract surgery during the follow-up period.

Statistical analysis

The sample size was calculated based on the ZAP Trial's primary endpoint of progression to acute or chronic primary angle closure in PACS eyes and is explained in more detail in the published study protocol.[7] Cox proportional hazards models were used to compare time to progression between treated and untreated eyes. Baseline measurements were compared by Student's t-test for continuous variables. For categorical variables, a Pearson's χ^2 or Fisher's exact test was adopted. All statistical analyses were conducted using Stata 13.1 (StataCorp LP, College Station, TX, USA). The significance level was set at 0.05 for a two-sided test.

Results

A total of 11,991 Chinese individuals aged 50 to 70 underwent the screening assessment between June 1, 2008 and December 31, 2008. Of the 1,087 (9.1%) participants identified as bilateral PACS, 889 of them agreed to be randomized and treated in the study.

The mean age of study participants was 59.3±5.0 years and 83% of them were female. There were no differences in BCVA, refraction, baseline IOP, gonioscopic grading, and cup-to-disc ratio between LPI-treated versus control eyes (Table 1). Almost all of the iridotomies were placed superiorly (99%) with average energy of 141 mJ. Localized hyphema occurred in 29% of LPI-treated eyes during the procedure, and one patient experienced a localized corneal burn (Table 1). Additionally, six participants had IOP ≥30 mmHg one hour after LPI, but all of their IOP levels returned to normal two hours after being administered medications (one drop of brimonidine 0.15% and 25 mg of methazolamide). No other adverse events occurred during or immediately following LPI treatment.

Lens grading was repeated at six months in 96 participants (10.8%), which showed good agreement in all categories (intraclass correlation coefficient all >0.71) except for PSC. Lens grades were similar between the two eyes at baseline and at each follow-up visit (Table 2). The average nuclear grades were slightly higher at 72 months among LPI-treated eyes (both NO and NC: 2.9 vs. 2.8, $p<0.001$, Table 2). However, the average cortical grades were lower in LPI-treated eyes (0.76 vs. 0.82, $p=0.030$, Table 2). There was no difference in average PSC grading between the two groups at 72 months.

At the end of 72 months, 169 eyes in the LPI group versus 152 eyes in the control group developed significant cataract. Nine eyes in each group received cataract surgery with five participants receiving surgery in both eyes. The total cumulative probability of reaching pre-defined cataract progression was 21.2% in LPI-treated eyes and 19.4% in control eyes ($p=0.401$). The incidence rate of cataract progression was 3.7 per 100 eye-years in LPI-treated eyes and 3.4

per 100 eye-years in control eyes. Although the overall risk of cataract progression in LPI-treated eyes appeared 10% higher compared to controls [HR=1.10 (95% CI 0.88-1.36), Table 3, Figure 1], this was not statistically significant. Furthermore, LPI did not significantly increase the risk of any particular subtype of cataract. The risk of cortical and PSC progression remained unchanged between eyes, and while the risk of nuclear sclerosis (NS) progression was approximately 50% higher in LPI-treated eyes, this was not statistically significant [HR=1.49 (95% CI 0.91-2.42), Table 4]. Factors associated with cataract progression included narrower angles and worse baseline vision ($p<0.001$ and $p=0.001$, respectively, Table 3). However, total energy used for LPI was not associated with greater risk of cataract progression in a multivariate analysis among treated eyes ($p=0.072$). Visual acuity at 72 months was similar in treated and untreated eyes at the final evaluation with BCVA of 0.29 and 0.28 on logMAR, respectively ($p=0.432$).

Discussion

Over six years of follow-up, 20% of participants with PACS had incident cataract progression in any lens region and 1% received cataract surgery, but prophylactic Nd:YAG LPI did not significantly alter the risk of cataract progression. Our findings strengthen the safety profile of the LPI procedure, as treated patients with narrow angles did not experience an accelerated rate of cataract development in the long term.

Previous publications have shown that intraocular surgery can increase the incidence of cataract.[11–14] The Collaborative Normal Tension Glaucoma Study reported a nearly two-fold increase in the incidence of cataract among participants who had received filtration surgery

versus untreated controls.[12] In the Advanced Glaucoma Intervention Study, rates of cataract surgery were higher for participants who underwent trabeculectomy surgery first in comparison to those who received argon laser trabeculoplasty first.[13] Moreover, the Collaborative Initial Glaucoma Treatment Study found three times the incidence of cataract surgery among participants who were randomized to initial filtration surgery as opposed to medical management.[14] The reasons for increased cataract formation after glaucoma surgery are poorly understood. However, it is thought that filtration surgery may alter the normal flow of aqueous humor across the lens, reducing nutrient delivery and thus interfering with the mechanisms that preserve transparency.[15] Other possible explanations for increased risk of cataract after intraocular surgery include postoperative inflammation in the eye, corticoid use after filtration surgery, and shallowing of the anterior chamber resulting in lens-to-iris or lens-to-cornea contact.[16]

Accelerated cataract progression after LPI has previously been proposed as a possible postoperative cause of decreased visual acuity.[3,5,6,17] Although some studies have attempted to assess this hypothesis, the existing research is limited by a short follow-up period, no lens grading, or by not having an appropriate control group. Additionally, most studies have used visual acuity as a surrogate marker of cataract progression. In a study with an average of two years of follow-up after argon laser iridotomy, visual acuity was worse than baseline in 15% of the patients, which was presumptively attributed to mild cataract progression.[3] Another study in an Asian population in Taiwan reported reduced visual acuity at six months after Nd:YAG LPI in 2.1% of cases.[17] A third study found no acute lens damage in the Nd:YAG-treated eyes, while 35% of lenses in the argon group had focal opacities.[4] In two more studies using similar pre-

defined cataract progression by LOCS grading, prophylactic LPI was shown to be a risk factor for predominantly cortical cataract in the Chennai Eye Disease Incidence Study and in the posterior subcapsular region of 60 fellow acute angle closure eyes from a study in Singapore (sequential argon laser pre-treatment and Nd:YAG LPI used).[5,6] Both studies were observational, and whether the development of cataract after LPI is due to the laser of the iridotomy or is simply part of the natural history of the participants remains uncertain.

In contrast, cataract progression based on LOCS III grades or cataract surgery, as well as visual acuity at the end of 72 months, was similar among treated and untreated eyes in the present study. Likewise, a retrospective study showed similar frequencies of cataract surgery over five years among people who received Nd:YAG LPI compared to those who did not, suggesting that LPI did not accelerate cataract progression.[18] Although we did find some evidence of increased NS progression in LPI-treated eyes, this slight increase was not statistically significant and could be due to chance. Besides the lack of statistical significance, only a small number of eyes progressed in total (47 treated eyes, 4.61% vs. 27 control eyes, 3.04%), and there was no clinically significant difference in BCVA between the groups at the last follow-up visit (difference in logMAR of 0.01). It should also be noted that cataract grading is a subjective measure, which may have partly contributed to this apparent increase in NS progression risk.

While cataract progression seems relatively minor when compared with the risk of an attack of acute angle closure, it is in fact of significant concern for glaucoma prevention programs in developing countries. If LPI worsens cataract significantly, clinicians could cause more blindness with widespread screening and LPI treatment rather than preventing vision loss in

countries where cataract surgeries are not readily available. The current findings are reassuring that prophylactic LPI does not lead to incident cataract formation.

One of the major strengths of our study is that LPI was performed in only one eye, so confounders at an individual patient level were controlled for. Furthermore, lens grading was standardized at each visit, and grading from previous visits was masked. Additional strengths include the study's low dropout rate, masked allocation, objective assessment of various parameters, and long-term follow-up and testing in an ethnic group with a high risk of primary angle-closure glaucoma. As for limitations of our study, it was not possible to fully mask the participants and the examiners due to the nature of the LPI procedure. Second, despite referring to LOCS III standard photographs, lens grading is inherently subjective, and the same graders were not necessarily used between visits over time. Therefore, it is possible that variability in the grading may have led to misclassification, reducing our power to detect a difference if one exists, or possibly creating subconscious bias to the observations. We attempted to address this limitation by assessing the degree of agreement of grading between baseline and six-month visits, assuming very limited lenticular changes within a short period of time. Grades of nuclear and cortical regions reached high agreement between two visits, but those for the posterior subcapsular region were poor. That said, the rate of PSC formation was extremely low overall, and misclassification of these cases is unlikely to have altered our study's overall findings. Finally, because the study population was Chinese, it is unknown whether our results are widely applicable to other racial or ethnic groups. Observed cataract progression rates after LPI may be affected by different underlying cataract progression rates found in different populations.[18]

In summary, at the end of 72 months, there were no differences in visual acuity and the rate of cataract progression between LPI-treated eyes and controls. This conclusion, along with previously published findings, demonstrate that there are low rates of acute complications from LPI.[4,18]

Contributors:

MH, PJF, and DSF conceived and designed the trial. MH, TA, PJF, and DSF were the chief investigators and oversaw the trial throughout. YJ and SH were trial examiners. DSC and BM monitored the data, performed analyses, and provided critical feedback to study design and activities. All authors contributed to the interpretation of data and decided on the content of the manuscript. DSC and JAK drafted and critically revised the manuscript for important intellectual content. All authors approved the final version.

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Competing Interests:

DSC and JAK are employees of Genentech, Inc.

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Table 1. Baseline characteristics of study population

	LPI-treated eye (n=889)	**Control eye (n=889)**
Age (year)	59.30±5.01	
Female (%)	737 (82.9%)	
BCVA (logMAR)	0.19±0.17	0.19±0.17
SE (diopter)	2.11±1.35	2.14±1.37
Baseline IOP (mmHg)	14.30±2.60	14.34±2.65
Total Shaffer score	5.33±2.37	5.34±2.40
CDR (ratio)	0.40±0.14	0.40±0.14
LPI location Superior (10-2 o'clock) Nasal or temporal	 877 (98.65%) 12 (1.35%)	
LPI total energy (mJ)	141.09±118.35	
LPI complications Hyphema Corneal burn IOP ≥30 mmHg	 257 (28.9%) 1 (0.11%) 6 (0.67%)	

BCVA, best-corrected visual acuity; SE, spherical equivalent by autorefraction; IOP, intraocular pressure; CDR, cup-to-disc ratio; LPI, laser peripheral iridotomy

Table 2. Lens status at baseline and follow-up visits

	Baseline		18 months		36 months		54 months		72 months	
	LPI (n=889)	**Control (n=889)**	**LPI (n=840)**	**Control (n=837)**	**LPI (n=784)**	**Control (n=778)**	**LPI (n=705)**	**Control (n=693)**	**LPI (n=650)**	**Control (n=625)**
NO	2.30±0.59	2.31±0.59	2.73±0.45	2.72±0.44	2.47±0.50	2.45±0.47	2.55±0.63	2.52±0.59	2.87±0.78	2.79±0.69
NC	2.18±0.57	2.19±0.58	2.53±0.44	2.52±0.43	2.47±0.53	2.45±0.51	2.63±0.65	2.59±0.61	2.92±0.79	2.84±0.71
C	0.83±1.16	0.84±1.16	0.79±1.16	0.82±1.19	0.91±1.15	0.93±1.16	0.80±1.05	0.81±1.06	0.78±1.13	0.81±1.13
PSC	0.11±0.30	0.12±0.33	0.06±0.15	0.08±0.27	0.03±0.30	0.03±0.26	0.05±0.34	0.03±0.24	0.05±0.41	0.05±0.40
Endpoint (number)										
Surgery			4	2	3	3	2	4	0	0
NO+NC			2	0	1	1	11	4	27	22
C			15	23	47	40	26	23	20	19
PSC			1	3	4	3	3	2	3	3
Total			22	28	55	47	42	33	50	44

NO, nuclear opalescence; NC, nuclear color; C, cortical; PSC, posterior subcapsular cataract; LPI, laser peripheral iridotomy

Table 3. Univariate and multivariate hazard ratios of cataract progression

	Univariate		**Multivariate**	
	HR (95% CI)	*p*	HR (95% CI)	*p*
LPI	1.10 (0.88-1.36)	0.415	1.09 (0.88-1.36)	0.437
IOP (mmHg)	1.00 (0.96-1.04)	0.910	1.00 (0.96-1.04)	0.816
BCVA (logMAR)	2.69 (1.47-4.92)	0.001	3.02 (1.55-5.91)	0.001
SE (diopter)	1.04 (0.96-1.12)	0.392	0.95 (0.87-1.04)	0.269
Total Shaffer score	0.90 (0.86-0.94)	<0.001	0.90 (0.86-0.94)	<0.001

HR, hazard ratio; LPI, laser peripheral iridotomy; IOP intraocular pressure; BCVA, best-corrected visual acuity; SE, spherical equivalent

Table 4. LPI and cataract progression at 72 months, by type of cataract

	NS	C	PSC
ICC	NO: 0.77 (0.71-0.82) NC: 0.79 (0.74-0.84)	0.71 (0.63-0.77)	0.10 (0.03-0.34)
Progression [n(%)]			
LPI-treated eye	41 (4.61%)	108 (12.15%)	11 (1.24%)
Control eye	27 (3.04%)	105 (11.81%)	11 (1.24%)
HR (95% CI)	1.49 (0.91-2.42)	1.01 (0.78-1.33)	0.99 (0.43-2.27)]

ICC, intraclass correlation coefficient; HR, hazard ratio; CI, confidence interval; NS, nuclear sclerosis; C, cortical; PSC, posterior subcapsular cataract