Editorial Commentary

Should we perform peripheral laser iridotomy in primary angle closure suspects: implications of the ZAP trial?

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Glaucoma is the leading cause of irreversible blindness globally. The morbidity due to disease is also quite high with an estimated 3.5% of population aged 40–80 years suffering from glaucoma (1,2). Broadly two types of primary glaucomas are identified, primary open angle glaucoma (POAG) and primary angles closure glaucoma (PACG). Angle closure glaucomas constitute a spectrum that include primary angle closure suspects (PACS, occludable angles), persons with primary angle closure (PAC, occludable angles with features indicative of trabecular outflow obstruction but absence of glaucomatous optic neuropathy) and finally PACG (presence of glaucomatous optic neuropathy). PACG is responsible for 31% of all cases globally, but the proportion has been reported to be higher in Asia at 40% (2). Data from population based studies in Asia show that PACG causes greater proportion of blindness than POAG (3).

Prophylactic laser peripheral iridotomies (LPI) are routinely offered to persons who are PACS and those with PAC (4,5). LPI is associated with to a widening of the anterior chamber angle and a deepening of the anterior chamber in eyes with PAC, while these parameters do not change significantly in eyes with PACG (6). Among PACS, this procedure is expected to decrease the risk of acute angle closure (AAC) attacks and delay the development of PACG. A report by American Academy of Ophthalmology concluded that LPI increases angle width and has good safety profile with most PACS eyes not receiving further interventions (7). Pearce *et al.* reviewed the clinical course of patients with PACS undergoing prophylactic LPI for five years and noted that 16.4% patients had progression; half progressing to PAC and the other half to PACG (8). In Scotland, the rates of LPIs have increased by 317%, from 19.7 to 82.2 per million in the five year interval between 2008 and 2012 (9). There are limited data on the efficacy of LPI in eyes with PACS and this remains a controversial issue in the scientific community with no clear guidelines. Prior studies evaluating LPI have often suffered from small sample sizes (10). He and colleagues, in the March 2019 issue of the Lancet, in a well-designed prospective study address this issue (11). In the single-centre, randomised controlled Zhongshan Angle Closure Prevention (ZAP) trial in urban Guangzhou, China, they assessed the efficacy of LPI in preventing PAC or AAC, in patients with bilateral PACS aged 50–70 years. They also observed the natural history of PACS, in eyes which did not undergo LPI.

Participants were screened for bilateral PACS through gonioscopy by trained ophthalmologists using standardized procedures. Static gonioscopy was done with single mirror lens system, with allowance of slight tilt of gonioprism for evaluation of angle. In case the trabecular meshwork was not visible on static gonioscopy, dynamic evaluation with four mirror system was done to check for presence of peripheral anterior synechiae (PAS). Patient was classified as PACS only if PAS were absent and the trabecular meshwork was not visible in ≥6 clock hours under non-indentation gonioscopy, along with absence of PAC or PACG, in both eyes. This is different from some earlier studies which used

270 degrees as the threshold. This was followed by optic disc evaluation. Eyes were eligible for LPI if vertical cup to disc ratio was less than 0.7, cup to disc asymmetry was no greater than 0.2, and neuroretinal rim width was greater than 0.1 vertical disc diameter. One randomly selected eye received LPI while contralateral eye served as the control, the allocation being revealed just prior to surgery to a masked research nurse. Follow-ups were planned at 2 weeks, 6, 18, and 36 months, and later extended to 54 and 72 months. The sample size was calculated as 700 in each arm; 889 eyes received LPI and an equal number of fellow eyes were controls. There was 22% attrition at 72 months with a majority 15% happening after 36 months, and this was in consonance with the sample size calculations. The primary outcome was the incidence of PAC at 72 months based one either of (I) raised IOP (>24 mm on two occasions); (II) PAS ≥1 clock hour; or (III) an AAC episode.

Among 889 persons, 10 achieved primary outcome in both eyes. The eye-wise incidence of any primary outcome in LPI treated eyes was 19 (4.19 per 1,000 eye-years), specifically 3 (0.66/1,000) for raised IOP, 15 (3.31/1,000) for development of PAS, and 1 (0.22/1000) for AAC. This was higher when compared with control eyes at 36 (7.97/1,000) for any primary outcome, 5 (1.11/1,000) raised IOP, 30 (6.64/1,000) PAS, and 5 (1.11/1,000) for AAC. Of the total six AAC events, four occurred after pupil dilatation. There was 47% reduction in rate of development of primary outcome (hazard ratio 0.53) with LPI compared to no surgery. Additionally, the probability of development of primary outcome increased with increased age, and shallower AC depth (limbal as well as central). No association was observed with higher IOP, Shaffer angles, lens thickness, provocative tests, or gender.

Secondary outcomes were presenting visual acuity, intra-ocular pressure, total angle width on gonioscopy, limbal anterior chamber depth, and any adverse events during laser peripheral iridotomy or at any follow-up visits. Overall mean sum of four Shaffer angle grades was higher in LPI eyes compared to control eyes. However, 49% angles remained closed 2 weeks after the LPI procedure. Paradoxically, the mean IOP was higher in LPI eyes compared to controls at all five follow-ups. None of the patients had vision loss. No adverse events were observed post-LPI and similar corneal endothelium density and LOCS scores were observed in both groups at 72 months follow-up. In terms of side effects, 10% of the patients reported glare after LPI, that was unrelated to site of the iridotomy.

Clinical significance

Progression from PACS to PAC

The rate of progression to any primary end point (raised IOP, PAS or AAC) among patients with PACS was much less than the anticipated from published literature. A previous study from India has reported 22% patients with PACS progressing to PAC over 5 years, while He and colleagues report only 4% (36/889) reaching any primary end point in 6 year follow-up (12). However, their results are consistent with another community based study from China, while a study from Mongolia has reported an even lower (1.6%) progression from PACS to PAC (13,14). A possible reason for this low progression rate could be taking a community based sample where asymptomatic cases could have been much detected earlier than usual. Dark room prone provocative tests were not helpful in identifying patients that are at risk of developing PAC.

Efficacy of LPI

Eyes undergoing LPI had 47% lower rate of development of any primary end point. The majority of end-points were non-sight-threatening in nature since a 45/55 (15/19 in LPI, 30/36 among controls) were development of PAS only. Of the six episodes of AAC (one in LPI, five among controls), four occurred after dilatation. The annual risk reduction (ARR) for development of PAC on account of LPI was 0.38%. The numbers needed to treat (NNT) was 44 to prevent one case of new PAC disease over 6 years, and 126 to prevent sight loss from glaucoma over a decade (assuming that among PACS patients progressing to PAC, 35% develop blindness in 5 years). This is a high NNT, especially in light of the observation that majority of PAC endpoints were not sight-threatening. As a comparison, Jefferson *et al.* reported NNTs for physical measures in preventing the spread of respiratory viruses as: handwashing more than 10 times daily =4, wearing gloves =5, wearing gowns =5; and handwashing, masks, gloves, and gowns combined =3 (15). With the low rate of development of primary end points and the limited number of clinical parameters under study, the authors could not provide information on the potential predictors of progression among PACS patients.

The study concludes that PACS patients should be informed about the low but definite future risk of angle closure glaucoma without LPI, and the higher risk of AAC with pupillary dilation. LPI should be an option in patients who need to undergo regular pupillary dilation

for other ocular conditions. Finally, all patients must be advised regular follow-up to assess for future need of LPI or glaucoma management.

Strengths and limitations

The trial clearly defined criteria for enrolment, exclusion and assessments. Adequate sample size was evaluated. The sample was selected from community through advertisements. Random allocation and masking of intervention were ensured. The study had a long follow-up period, which was increased in view of low event rates. Adequate data safety mechanisms including an independent biostatistics centre were in place. The trial followed the recommended guidelines to minimize bias including intention-to-treat analysis, McNemar's tests for paired eyes, and cox-proportional hazards model to assess outcomes over follow-up time. Authors lowered the threshold to statistical significance to $P<0.025$ in view of few outcomes.

The low progression rates may be specific to the populations under study and may not be generalizable to other populations. The low event rates, along with a limited number of baseline clinical parameters under evaluation, also mean that the authors are unable to derive any definite conclusions about risk factors for progression from PACS to PAC, and for identifying high-risk PACS patients who may benefit most from LPI. The other important factors that have not been evaluated include impact of corneal thickness on IOP measurements, diurnal IOP fluctuation and family history of PAC glaucoma.

Conclusions

He *el al.*, in a well-designed study, provide comprehensive evidence on the utility of LPI among patients with PACS for prevention of development of PAC. While the treatment is effective in preventing progression, given the low incidence of development of PAC both in untreated and treated groups and the even lower rate of sight-threatening events, the implementation of LPI in glaucoma screening programs is not recommended and needs further research. The low rates of progression of PACS may be unique to this population and ophthalmologists are advised to take this into consideration when making clinical decisions regarding LPI for patients with PACS in their settings. We also recommend that in PACS eyes which have not undergone laser, should be educated about the symptoms/signs of an acute attack of angle closure and may be advised to instill 2% pilocarpine eye drops in such a situation, if immediate access to health care services is not available.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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