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EDITORIAL

Prevention of angle-closure glaucoma: balancing risk and benefit

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Primary angle-closure glaucoma (PACG) is an important, preventable cause of visual loss. PACG affects 20 million people, and has blinded over 5 million globally [1]. Although it is well established that Asian people are at greater risk than white people of European origin [2, 3], an estimated 1.6 million white Europeans, 581,000 white US citizens and 130,000 white Britons have visual field loss from PACG [4]. The results of two major clinical trials have transformed the evidence-base informing management of PACG. The EAGLE trial clearly demonstrates that anyone with PACG, and those with an intraocular pressure (IOP) > 30 mmHg resulting from primary angle-closure (PAC), should be offered clear lens extraction as the first intervention. This offers better disease control (better pressure control with less medication), better quality of life, and is more cost effective when compared to the standard care of laser peripheral iridotomy (LPI) [5].

In the context of the large numbers of people affected, it is not surprising that, in 2005, 75% of UK consultant ophthalmologists when questioned said they would offer LPI as a preventive treatment to patients at risk of PACG [6]. However, this strategy is probably a well-meaning extrapolation of the unquestioned importance of performing LPI in patients suffering acute angle-closure (AAC) [7]. However, the strategy of offering prophylactic LPI was not based on evidence. Indeed, one large randomised controlled trial in Mongolia showed no benefit for a package of screening and prophylactic LPI [8]. Furthermore, current policy strongly advises community optometrists to refer all patients who may be at risk of PACG to see an ophthalmologist [9]. In this context, "at risk" is defined as a limbal chamber depth grade of </=25% of peripheral corneal thickness [10]. These people are assumed "primary angle-closure suspects" (PACS) [11].

The Zhongshan Angle-closure Prophylaxis (ZAP) study provides the first clear insights into the natural history of PACS, and of the benefits of prophylactic LPI, in one of the highest risk populations on earth—Chinese people over the age of 50. The trial showed that, at the end of the planned 3-year follow-up period, there was no detectable benefit from prophylactic LPI (36 month hazard ratio (HR) = 0.90, 95% CI 0.44–1.85; $p = 0.777$). The reason for this finding was an exceptionally low rate of incident PAC or PACG. The study was extended for a further 3 years, at which time, it was found that LPI halved the risk of incident PAC (72 month HR = 0.52; 95% CI 0.30–0.91; $p = 0.023$). There were no incident cases of PACG over the 6 year follow-up. There were only 5 untreated eyes and one treated eye that suffered AAC. In eyes that had not undergone prophylactic LPI, this equated to a risk of 1.1 eyes per 1,000 years. There were 5 untreated and 3 treated eyes that were found to have a sustained IOP elevation (>21 mmHg). The bulk of PAC disease identified in the ZAP trial were defined by peripheral anterior synechiae (PAS), affecting 15 treated and 30 untreated eyes [12]. It is important to recognise that, while elevated IOP does present a measurable risk for visual field loss [13, 14], the risk of sight loss associated with PAS is unknown.

With new data from the EAGLE and ZAP trials, the Royal College of Ophthalmologists approved a proposal from the authors to draw up guidelines for management of PACG and PAC in the UK. The evidence synthesis and writing of draft guidelines were completed in March 2020. The events of the following months have brought UK healthcare under pressure not seen since the foundation of the National Health Service. The huge backlog for routine care makes it vital that clinical capacity be used for maximum benefit. The results of the LiGHT trial brings selective laser trabeculoplasty (SLT) clearly into the repertoire of treatments that should be offered to the many patients with ocular hypertension and early primary open-angle glaucoma [15]. There is an opportunity cost for glaucoma laser treatment capacity. Offering prophylactic LPI which appears to be of marginal benefit in a high-risk Asian population, or offer SLT, which is proven in terms of its medical performance and health economics. SLT as first treatment has a 97% probability of being more cost effective than eye drops first at a willingness to pay of £20 000 per quality-adjusted life-year gained. In contrast, preliminary calculations for prophylactic LPI suggest a 7% probability of being cost effective at a willingness to pay £20 000 per quality-adjusted life-year in the UK (Ramjee, Foster, currently unpublished).

Looking at the performance of prophylactic LPI from the perspective of numbers needed to treat (NNT), the ZAP study authors calculated that, in a high-risk Chinese population, the NNT to prevent one case of PAC over 6 years was 44. Making cautious extrapolation to prevention of glaucoma, the NNT is 126 treated to prevent one case of glaucomatous field loss over 10 years. In the UK, the NNT's will be larger, probably by a factor of 2–3, if one takes the ratio of AAC occurring in Caucasians to East Asians [16]. To quote from the ZAP trial manuscript, *"LPI should only be offered to those with the (very) highest risk of PACG"*.

Furthermore, the impact LPI has on patients should not be underestimated. In a focus group, patients unanimously reported great anxiety before LPI, and reported pain (see Table 1).

Operationalising this recommendation in the NHS in 2021 requires a pragmatic balance of caution, and a rational appraisal of facts. Not only does prophylactic LPI offer a poor return on time, effort and expenditure, it diverts resources from other more cost-effective interventions. Furthermore, only a proportion of patients referred for assessment will have been correctly classified as PACS, with the false positive referrals unnecessarily absorbing further time and manpower.

In this context, we reinforce the message that prophylactic LPI should only be offered to those individuals at highest risk. Table 2 lists the characteristics that capture this level of risk. We see this recommendation not as a final, definitive policy for PACG management in the UK, but as an important stage in its evolution.

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Table 1. Patient experience with laser peripheral iridotomy.

Participant 1
"I was quite apprehensive I have to say you put me absolutely at ease. I was quite surprised when you described it to me as to what it would be, and the sort of tingling the type of feeling that I would feel. It was totally different than that I mean it genuinely felt like an electric shock to the back of the eye socket and you had me recoiling at the time. When you touch a light switch and you get a shock, it was like that, through the eyeball"
Participant 2
"My experienced was it was painful, and I wanted to stop because it was really painful it was uncomfortable but I thought okay he's done this millions of times, he knows what he's doing maybe it's just normal. But at some point I pulled away from this, just because it was so intense. I thought that I would have an anaesthetic and I wouldn't feel anything but it was the opposite experience, so it was very painful. I had more anaesthetic drops, then, and it was then better, but if I could avoid it I wouldn't want to have it again, it was not pleasant for me at all. It was awful like someone shocked into my eye socket. It had the stinging effect like you got stung by a bee or something, just the impact of it was excruciating".
Participant 3
"I guess, initially, I was thinking I don't even know if I want this, it sounds horrific. I went in had it and would say I didn't actually feel a thing. It was nothing like my expectation of it, I didn't have any discomfort afterwards".
Participant 4
"I'd say I had a fairly easy pain free experience I know the second I felt slightly more than the first but not to the extent that it sounds as though some others of you"
Participant 5
"I actually feel like the others it was like being shot, it was agonizing it really was but for me, there was no alternative and well the alternative was losing the sight potentially in my right eye, so there was no choice, and I was really grateful to have it done"

Table 2. "PACS PLUS" - Criteria for referral of people with suspected occluded angles to Hospital Eye Service or secondary care provider.

Angle criteria
Either—an anterior segment OCT showing irido-trabecular contact (ITC)
Or—a limbal chamber depth grade <25%
PLUS: one of the following criteria
• People with only one "good eye" in which deterioration of vision may threaten independent living or livelihood.
• Vulnerable adults who may not report ocular or vision symptoms
• Family history of significant angle-closure disease
• High hypermetropia (>+6.00 dioptres)
• Diabetes or another condition necessitating regular pupil dilation
• Those using antidepressants or medication with an anticholinergic action
• People either living in remote locations (such as foreign aid workers, armed forces stationed overseas or oil rig workers etc.) where rapid access to emergency ophthalmic care is not possible
The finding of "PACS PLUS" should trigger referral to the Hospital Eye Service
"PACS MINUS"
If an individual has the angle-characteristics specified above but none of the "plus" criteria, and does not meet NICE glaucoma referral guidelines, they should be advised to seek an annual NHS sight test.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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