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Research Progress on Preventive Laser Peripheral Iridotomy in Patients with Primary Angle-Closure Suspect

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Abstract

Glaucoma is one of the most serious ophthalmological diseases threatening vision globally. Among them, Primary Angle Closure Glaucoma (PACG) is the most common type in China. Primary Angle Closure Suspect (PACS) represents the earliest morphological stage of pupillary block, serving as an early phase in the chain of PACG onset. Early screening for this population is a critical node to prevent further progression to PACG and thereby avoid irreversible visual field damage. Laser peripheral iridotomy (LPI) is widely regarded as the most common treatment modality for PACS patients. Performing LPI can prevent further closure of the anterior chamber angle and fundamentally resolve pupillary blockage. However, recent prospective clinical studies have shown that while LPI significantly reduces the conversion rate from PAC/PACG, due to the extremely low endpoint event conversion rate inherent to the PACS population and its large base size, the preventive efficacy of LPI is very low. Therefore, it is not recommended to widely apply prophylactic LPI to this group. Although LPI is considered a safe and effective non-invasive procedure, it does not represent complete harmlessness; the complications pose significant risks to patients. Therefore, careful differential diagnosis of indications and comprehensive judgment regarding whether to perform prophylactic LPI should be made. It is advocated to implement risk stratification for PACS patients and consider using prophylactic LPI for those with high-risk factors. Currently, research on high-risk factors is still ongoing. In the context of actively promoting cataract surgery, early cataract extraction for PACS patients has become an undeniable new trend.

Keywords

Primary Angle Closure Suspect, Laser Peripheral Iridotomy, End Event Conversion Rate, Preventive Efficiency, Cataract Surgery

1. Introduction

Primary angle-closure glaucoma (PACG) is one of the leading ophthalmic diseases causing irreversible visual impairment worldwide. Among various types of glaucoma, primary angle-closure glaucoma is more prevalent in Asia and is the most common type of glaucoma in China [1]. Over the past two decades, systematic reviews and meta-analyses have shown that the global prevalence of PACG is approximately 0.6%, with the highest prevalence in Asian regions at about 0.7% [2]. It is estimated that among Asian populations over the age of 40, there are approximately 12.3 million patients, accounting for about 71% of global PACG patients [3]. By 2025, the total number of global PACG patients has exceeded 17 million, and it is projected to surpass 26 million by 2060 [2]. In China, regional epidemiological surveys indicate a prevalence of angle-closure glaucoma of 2.03% in the population over 40 years old.

2. The Anatomical Characteristics of Primary Angle-Closure Suspect

Primary angle-closure glaucoma is a disease caused by the acute or chronic closure of the anterior chamber angle, leading to obstruction of the normal outflow pathway of aqueous humor, resulting in acute or chronic intraocular pressure (IOP) elevation. This, in turn, causes irreversible visual function damage and ultimately leads to blindness [4]. According to the classification system of the International Society of Regional Epidemiology in Ophthalmology, Foster [1] *et al.* divided the evolution process of primary angle-closure glaucoma into three stages:

1) Suspected Primary Angle Closure (PACS): Refers to narrow anterior chamber angles with normal IOP.

2) Primary Angle Closure (PAC): Refers to narrow anterior chamber angles accompanied by peripheral anterior synechiae (PAS), resulting in transient IOP elevation but no optic nerve or visual field damage associated with glaucoma.

3) Primary Angle-Closure Glaucoma (PACG): Refers to IOP elevation caused by angle closure that has already caused irreversible damage to the optic nerve and visual field [5].

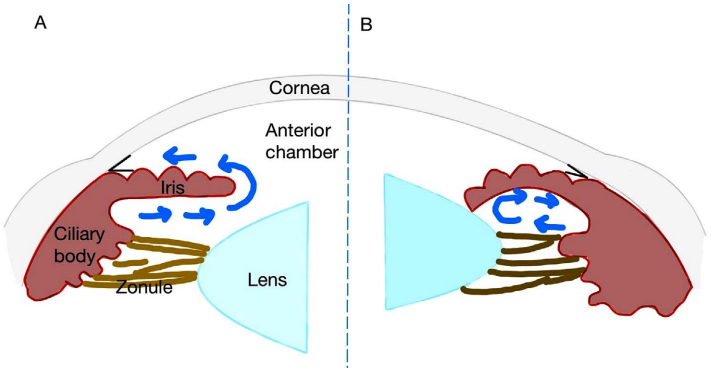
Primary angle-closure suspect (PACS) represents the earliest stage of angle closure. Although intraocular pressure elevation or glaucomatous optic neuropathy has not yet occurred, the anatomical structure already carries high-risk factors for angle closure. Without intervention, PACS may gradually progress to primary angle closure (PAC) or even primary angle-closure glaucoma (PACG), leading to sustained intraocular pressure elevation, optic nerve fiber layer damage, visual

field defects, and ultimately potential blindness. Previous studies on the progression rate of PACS have shown variability due to differences in study populations and follow-up durations. The study by Ji *et al.* [6] reported that approximately 14% of patients with PACS progressed to PAC (defined as the development of peripheral anterior synechiae or elevated intraocular pressure) over a follow-up period of 6.2 years. In the study by Thomas *et al.* [7], an epidemiological study with a 5-year follow-up showed that 22% of PACS patients progressed to PAC within 5 years. The study further indicated that among those who progressed to PAC, 28.5% subsequently developed PACG within 5 years. Therefore, increasing attention and research on the PACS population is a critical intercept point for the prevention and treatment of angle-closure glaucoma. Early screening and risk stratification are of great significance in reducing the rate of blindness.

3. The Formation Mechanism of Primary Angle-Closure Suspect

Primary angle-closure suspect (PACS) is not an independent disease but rather an early stage in the pathogenic cascade leading to primary angle-closure glaucoma (PACG). As **Figure 1** shows, the hallmark of PACS is an abnormal anterior segment anatomy, which predisposes the peripheral iris to contact and obstruct the trabecular meshwork, yet without causing intraocular pressure (IOP) elevation or optic nerve damage. Its core mechanisms can be broadly categorized into pupillary block and non-pupillary block types. Pupillary block is the most common pathogenic factor; it occurs when the posterior surface of the iris adheres closely to the anterior surface of the lens, impeding the flow of aqueous humor from the posterior chamber to the anterior chamber. This leads to increased posterior chamber pressure, which pushes the peripheral iris forward, narrowing or even closing the anterior chamber angle. Studies have found that most primary angle-closure glaucoma cases exhibit pupillary block anatomy. In Chinese patients with primary angle-closure glaucoma, 92.8% have pupillary block factors, and pure pupillary block-induced angle closure accounts for 38.1% of cases [8].

Non-pupillary block factors are primarily attributed to the inherent crowding within the ocular structure, which directly compresses the anterior chamber angle. These include conditions such as a highly folded iris, abnormal lens positioning, choroidal expansion, and laxity of the suspensory ligaments. As individuals age, the lens thickens and shifts anteriorly, occupying space within the anterior chamber, thereby constituting a mechanism for the progression of PACS. Recent research has also demonstrated that choroidal thickening can push the iris-lens diaphragm forward, further inducing alterations in the anterior chamber and the angle [9]. Wang *et al.* [8] conducted an in-depth investigation into the pathogenesis of primary angle-closure glaucoma using ultrasound biomicroscope (UBM). Their findings revealed the coexistence of multiple mechanisms, highlighting the primary mechanisms underlying angle closure in the Chinese population.

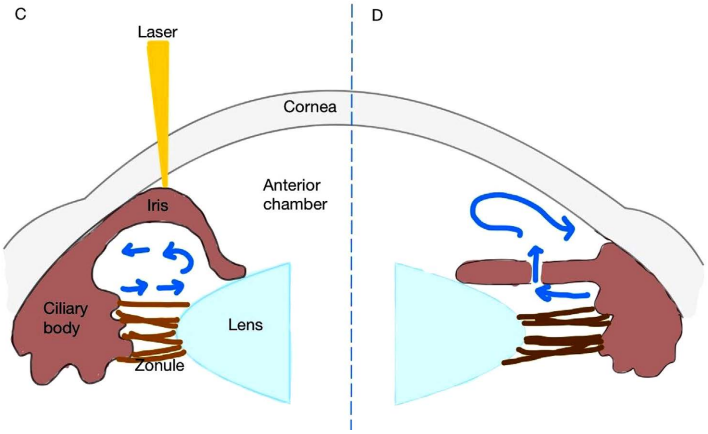


(The blue part indicates the lens; the dark red part indicates the ciliary body and iris; the yellow part indicates the zonule; and the blue arrows indicate the aqueous humor circulation pathway.)

Figure 1. Aqueous humor flow in normal vs blocked states. (A) Normal state; (B) Blocked state.

4. The Clinical Efficacy of Laser Peripheral Iridotomy

Preventive laser peripheral iridotomy (LPI) is currently the most commonly used intervention to prevent the progression of PACS [9] [10] (Primary Angle Closure Suspect). The mechanism of LPI involves the precise focusing of laser energy on the peripheral iris, which creates a small opening that allows the posterior chamber pressure to rapidly equilibrate with the anterior chamber pressure. As **Figure 2** shows that this restores the normal physiological outflow of aqueous humor, resolves pupillary block, eliminates iris bombe [11], deepens the anterior chamber depth, and widens the angle width. By fundamentally addressing the pupillary block mechanism, LPI serves as a critical measure for preventing the progression of PACS and its further development into angle-closure glaucoma.



(Blue regions indicate the lens, dark red regions indicate the ciliary body and iris, brown regions indicate the suspensory ligaments, bright yellow regions indicate the laser beam, and the blue arrows indicate the pathway of aqueous humor circulation.)

Figure 2. Comparison of Anterior Segment Anatomical Structures and Aqueous Humor Circulation Before and After LPI. (C) Pre-LPI: Iris bombe, aqueous humor circulation is obstructed. (D) Post-LPI: Iris bombe is eliminated, aqueous humor circulation is restored.

Key Findings from Longitudinal Studies:

Thomas *et al.* [7], 2003: Conducted a 5-year prospective cohort study involving 526 patients diagnosed with PACS. The natural progression risk observed indicated a PAC development rate of 6.08% over 5 years. This study highlighted a crucial perspective: while LPI demonstrates a high success rate in preventing further progression of PACS, the overall progression rate must be considered. Universal recommendation of LPI for all PACS patients may not be appropriate.

Zhongshan Angle Closure Prevention (ZAP) Study [12]: In an initial 6-year prospective study later extended to 14 years, this trial recruited 889 bilateral PACS patients (meeting criteria: ≥180˚ angle closure in both eyes, no PAS or elevated IOP) aged 50 - 70 from community residents. A single-eye randomized controlled trial was performed where one eye received LPI and the contralateral eye served as a control. The results demonstrated a statistically significant reduction in PAC progression risk, with a 69% decrease in the risk of developing PAC. The results showed that the absolute event incidence (per 1000 eye-years) was lower in the LPI group than in the control group (4.19 vs 7.97).

Ana-LIS Study (Singapore) [13]: Similar to ZAP, this study investigated the effect of preventive LPI on asymptomatic narrow-angle patients recruited from Singaporean ophthalmology clinics. The incidence of primary endpoints (PAC or acute attacks) in the LPI group was significantly lower than that in the control group. Specifically, the LPI group exhibited a 5% incidence rate (4.19 per 1000 eye-years), compared to a 9% incidence rate (21.84 per 1000 eye-years) in the control group. Over a 5-year follow-up, LPI treatment reduced the risk of PAC/PACG development by 45% compared to control eyes.

Patrick Ji *et al.* [6], Recent Systematic Review and Meta-Analysis: Established strict inclusion criteria, incorporating 2 randomized controlled trials and 3 observational studies. By integrating data from multiple studies, it was found that patients receiving LPI treatment significantly reduced the risk of PAC progression, achieving an overall risk reduction factor of 2.49.

2010 Randomized Controlled Trial in Mongolian Population [14]: This large-sample study recruited 4725 Mongolian volunteers aged 50 and above. The conclusion indicated no statistically significant difference between the preventive LPI group and the control group in reducing the incidence of PACG.

Interpretation and Considerations:

Despite the significant efficacy of preventive LPI in reducing PACS progression observed in the aforementioned studies, an important fact cannot be ignored. The ZAP [15] study also reported an overall conversion rate (PACS convert to acute or chronic PAC) of less than 1%, indicating that only a small proportion of patients benefit from this intervention. This suggests that universal preventive LPI may not be suitable for all PACS patients. Similarly, the ANA-LIS [13] trial reported a Number Needed to Treat (NNT) of 22, meaning that 22 patients need to be treated to prevent one endpoint event (progress to PAC). This leads to the same conclusion as ZAP: the overall incidence of endpoint events is low, and the preventive efficacy is limited.

It is not recommended to universally apply preventive LPI to asymptomatic, simple PACS patients, but this does not entirely negate the efficacy of LPI as a preventive treatment. In a follow-up study extending the ZAP trial, Yuan *et al.* [16] identified baseline higher intraocular pressure, shallower corneal edges, and shallower central anterior chamber depth as risk factors for PACS progression, after controlling for various other variables. In an earlier study, Le *et al.* [17] observed that, over a span of 25 years, 50% of acute ACG patients who either received no treatment or used pilocarpine 1 - 2 times daily in the contralateral eye experienced acute attacks. Conversely, among 54 patients who underwent preventive LPI within the same timeframe, only one case of acute attack was reported. This suggests that a history of acute ACG attacks may be a high-risk factor.

The conversion rate from PACS to PAC is inherently low, resulting in poor preventive efficiency for LPI when applied on a large scale. However, this conclusion pertains to broad population-level interventions; in clinical practice, individual patient differences must be considered. For PACS patients with clear high-risk factors, proactive preventive LPI is crucial for blindness prevention. For those with a confirmed family history of glaucoma or those unable to maintain regular follow-ups, preventive LPI treatment can be considered [15]. Due to the low number of positive conversion cases, it is challenging to effectively analyze PAC risk, necessitating further research to identify which PACS individuals benefit most from preventive LPI.

5. The Complications of Laser Peripheral Iridotomy

Laser peripheral iridotomy (LPI) is a non-invasive procedure that offers several advantages, including minimal complications, reduced patient discomfort, and lower economic burden. It is considered a safe and effective method for preventing the progression of PACS. However, it is not entirely without risk, and certain complications warrant careful attention.

1) Transient Postoperative Intraocular Pressure (IOP) Elevation

This is the most common complication following LPI, with an incidence rate reported to be approximately 5.7% to 40.0%. The elevation in IOP can be associated with factors such as the choice of surgical technique and the presence of abundant iris pigment. Jiang *et al.* [18] found that patients with shallower central anterior chambers had an increased risk of experiencing an IOP spike within the first hour after surgery. However, other studies, like that of Liang [19], have indicated that there may not be a significant correlation between laser energy levels and IOP elevation.

2) Cataract Progression

This is a primary cause of visual acuity decline in PACS patients who undergo LPI. Research by Vijaya *et al.* [20] revealed that the risk of cataract progression is particularly pronounced in elderly patients and female patients with diabetes.

3) Other Potential Complications

Corneal Endothelial Cell Damage [21]: LPI can potentially harm the corneal

endothelial cells, which are crucial for maintaining corneal clarity and function.

Decreased Subjective Visual Quality [22] [23]: Some patients may experience a reduction in visual quality post-procedure, which can affect daily activities and overall visual comfort.

In summary, while LPI remains a common and effective treatment for PACS, it is essential to acknowledge the potential for a range of complications. A thorough understanding of the surgical indications and meticulous surgical technique is required to mitigate these risks and ensure optimal patient outcomes.

6. The Emerging Trends in Primary Angle-Closure Suspect Treatment

In the context of an active promotion of cataract extraction surgery and the continuous maturation of surgical techniques, early cataract extraction to reduce the risk of angle closure represents an important emerging trend for PACS patients with mild cataract. Removing the thickened lens not only eliminates pupillary block and fundamentally alters the anatomical morphology of the eye but also yields significant improvements in visual acuity, a benefit that cannot be underestimated. Yan *et al.* [24] conducted a prospective study involving 144 PACS patients with mild cataracts, with a 2-year follow-up. Through a comparative group analysis, they found that, compared to LPI, early cataract extraction induced more significant changes in related parameters such as central anterior chamber depth (ACD), angle opening distance (AOD500), and trabecular-iris angle (TIA). More critically, after a 2-year observation period, no residual angle closure was observed post-cataract surgery. This study provides clinical evidence supporting early cataract extraction as an option for PACS patients with mild cataract. It should be noted that this evidence does not apply to all PACS patients; for those without cataract but with other risk factors, LPI remains a reasonable treatment choice.

7. Summary

Primary angle-closure suspect (PACS) represents the earliest stage in the pathogenic cascade of primary angle-closure glaucoma. Although there is no visual impairment at this stage, anatomical abnormalities are already present, making the prevention of further progression crucial for averting irreversible visual loss. While preventive laser peripheral iridotomy (LPI) can effectively halt the progression of PACS and is a relatively safe therapeutic measure, the extremely low probability of PACS converting to PAC/PACG raises concerns about its overall preventive efficacy. Consequently, universal application of LPI across all PACS individuals may be inappropriate. Stratifying PACS patients based on risk, identifying those with a higher likelihood of conversion, and implementing selective preventive LPI holds significant clinical importance. We anticipate further research to elucidate specific high-risk factors. Notably, recent attention has turned towards early cataract extraction for PACS patients, which may offer greater benefits.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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