**RESEARCH PROTOCOL**

**Title:** Correlation between clinic-measured intraocular pressure (IOP) and disease progression in primary angle closure glaucoma (PACG)

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# Abstract of research

Primary angle-closure glaucoma (PACG) is an eye disease characterized by closure of the anterior chamber drainage angle by appositional or synechial approximation of the iris against the trabecular meshwork, blocking the access to aqueous humor, resulting in an elevation of the intraocular pressure (IOP) followed by the progressive development of irreversible glaucomatous optic neuropathy.1;2 The prevalence of angle closure glaucoma was found to be highest amongst Chinese (1.26%), affecting over 7 million Chinese by 2010.3 Angle closure glaucoma was reported to be responsible for the vast majority (91%) of bilateral glaucoma blindness in China.4 In Hong Kong, glaucoma remains the most important cause of irreversible blindness, accounting for almost one-quarter of all cases of irreversible blindness (Hong Kong Hospital Authority statistics 2003).

The treatment of PACG involves the lowering of IOP by drugs, laser, or surgery.5 Conventionally, the target of treatment is to lower IOP to within the ‘normal’ range, i.e. below 21 mmHg, whether in clinical practice or as a criterion for treatment success in PACG research. Recent clinical trials in primary open angle glaucoma (POAG) revealed that even within the normal range of IOP, maintaining the IOP within a lower bracket conferred additional clinical benefit in terms of less visual field deterioration.6 This has been cited as evidence for the need to aim for a target IOP lower than the population mean (16 mmHg) in POAG eyes, especially the more advanced cases. Similar published data are not available for PACG. Our earlier pilot study suggested a similar relationship between IOP and visual field progression in PACG, but our sample size, follow up duration, and study design did not allow a firm conclusion (Free paper presentation at the Annual Meeting of the American Academy of Ophthalmology in 2007). A more recent study by Sharmini et al7 also suggested a similar relationship in PACG, but the retrospective nature and the suboptimal definitions of disease progression in this study resulted in only a suggestive conclusion.

This study aims to clearly define the correlation between IOP and disease progression in treated PACG, especially within the ‘normal’ range of IOP. Disease progression is defined in accordance with internationally-recognized standards as for POAG, and also with the help of latest imaging technology and analysis software (Stratus optical coherence tomography – Stratus OCT). The results of this study will have huge impact on the treatment strategy for PACG.

**Primary objective:**

1. To delineate the correlation between clinic-measured IOP and disease progression in treated PACG, especially within the normal range of IOP (6 – 21 mmHg)

**Secondary objectives:**

1. To determine whether different means of achieving a particular IOP (IOP-lowering drugs versus lens extraction versus trabeculectomy versus combined procedures) may have an effect on disease progression in PACG
2. Subgroup analysis may help determine which subgroup(s) of patients, e.g. more advanced disease, may require lower IOP for disease stabilization
3. To help clinicians identify an evidence-based target IOP for their PACG patients

**Research plan and methodology:**

The study protocol complies with the Declaration of Helsinki (version 2000).

The study protocol complies with the ICH-GCP guidelines.

Informed consent will be obtained from all participating patients.

**Study sites**

Hong Kong Eye Hospital (HKEH), Kowloon

Prince of Wales Hospital (PWH), Shatin

**(a) Study subjects**

**PACG patients**:

We aim to recruit 500 Chinese PACG patients at Hong Kong Eye Hospital and Prince of Wales Hospital. To cover the loss of subjects who have withdrawn from the study, the planned sample size currently would be 575 subjects, including 44 subjects from our ongoing study titled ‘*To determine the role of vascular changes in optic nerve head, retina, and choroid, in the pathogenesis of glaucoma’* (Ref.: KC/KE-17-0099/ER-3) who had provided informed consent for this study.

**Recruitment and diagnostic criteria**

Inclusion criteria

* On darkroom gonioscopy, at least 180º of iridotrabecular contact (ITC) obliterating posterior pigmented part of trabecular meshwork, whether synechial or appositional, segmented or continuous, in the presence of a patent peripheral iridotomy;
* Requiring intraocular pressure (IOP)-lowering medications, or IOP of above 21 mmHg without IOP-lowering medications;
* Visual field loss compatible with glaucoma and / or glaucomatous optic disc changes;
* Minimal criteria for glaucomatous visual field defect as per published standard:8 glaucoma hemifield test outside normal limits, pattern standard deviation with a P value of <5%, or a cluster of ≥3 points in the pattern deviation plot in a single hemifield (superior or inferior) with P value of <5%, one of which must have a P value of <1%. Any one of the preceding criteria, if repeatable, was considered sufficient evidence of a glaucomatous visual field defect;
* Characteristic optic disc changes include vertical cup-disc ratio > 0.5, discrepancy of vertical cup-disc ratios between the 2 eyes of > 0.2, thin or notched neuroretinal rim, disc hemorrhage, and / or retinal nerve fiber layer wedge defect;
* Patient able and willing to give informed consent to participate.

Exclusion criteria

* Any secondary causes of angle closure or ocular hypertension, such as:
* Uveitis
* Neovascularization of iris / angle, e.g. from diabetes or CRVO
* Iris / ciliary body cysts
* Posterior segment mass effect, e.g. posterior segment hemorrhage or tumor
* Marfan syndrome
* Axenfeld-Rieger syndrome
* Trauma
* Steroid-induced
* Iatrogenic, e.g. after vitreoretinal surgery

One eye of each patient will be selected for inclusion in study, and this is selected by using a random number table at the time of recruitment (odd numbers – left eye; even numbers – right eye).

**(b) Data collection at recruitment**

The following information will be collected for each patient:

* Hospital number (No Hong Kong ID number will be collected)
* Date of birth
* Date of diagnosis of PACG
* Date of any previous acute primary angle closure (APAC)
* Date of any previous argon laser peripheral iridoplasty (ALPI)
* Date of laser peripheral iridotomy (PI)
* Date of any previous cataract surgery
* Date of any previous glaucoma surgery
* Any co-existing cataract, diabetic retinopathy / maculopathy, age-related macular degeneration, or other eye diseases that may affect visual acuity or visual field

A systemic medical history is taken, with specific reference to history of:

* Hypertension (HT)
* Diabetes mellitus (DM)
* Hyperlipidemia (HL)
* Ischemic heart disease (IHD)
* Cerebrovascular accident (CVA)
* Cancer
* Smoking
* Number of cigarettes per day
* Number of years of smoking
* Number of years since quitting smoking
* Any secondary smoking
* Any family history of PACG / glaucoma

Ophthalmic examinations and investigations at recruitment:

* Date of study examination
* Best-corrected Snellen visual acuity and spherical refractive error
* Clinic-measured intraocular pressure (IOP) - measured with a Goldmann applanation tonometer on a slit-lamp biomicroscope. The reading in mm Hg is rounded to the next higher integer. Each measurement is repeated, and if the two readings differ by 3 mm Hg or more, a third measurement is taken. The median of the two or three measurements becomes the IOP determination.
* The number of IOP-lowering drugs (topical and systemic)
* Central corneal thickness and axial length by ultrasonography
* Central corneal endothelial cell count by specular microscopy (SM)
* Gonioscopic examination of angle structures, and grading by the Shaffer system
* Anterior segment imaging by Anterior Segment Optical Coherence Tomography (AS-OCT) using the Visante™ OCT (Carl Zeiss Meditec, Dublin, California, USA). The Irido-Corneal Tools Module of the Visante™ OCT will be used to document the following drainage angle parameters: Angle Opening Distance (AOD), the Trabecular Iris Space Area (TISA), the Angle Recess Area (ARA), the Scleral Spur Angle and the Trabecular Iris Contact Length (TICL).
* Vertical cup-to-disc ratio, and other optic disc changes suggestive of glaucoma
* Optic disc imaging by Cirrus™ Spectral Domain HD-OCT (Carl Zeiss Meditec, Dublin, California, USA)
* Automated perimetry using the Humphrey Field Analyzer II (Carl Zeiss Meditec, California, USA) (central 24-2 threshold test, Sita standard strategy, size III white stimulus, with the foveal threshold test turned on)
* Retinal nerve fiber layer thickness measurement by Optical Coherence Tomography III (OCT III) imaging system (Stratus OCT, Carl Zeiss Meditec, Dublin, California, USA)

**(c) Data collection at follow up**

All recruited patients will be followed up in the Glaucoma Clinics at Hong Kong Eye Hospital and Prince of Wales Hospital for 5 years. Gonioscopy for angle assessment and documentation of optic nerve head appearances (including vertical cup-to-disk ratios) will be performed at least once a year as in standard clinical practice. During follow up, patients will be prescribed IOP-lowering drugs, and advised surgery (phacoemulsification, trabeculectomy, or combined phaco-trabeculectomy), as clinically indicated. The goal of IOP-lowering treatment is to achieve an IOP of 21 mmHg or below, as in standard clinical practice.

Documentation of IOP

All recruited PACG patients will be seen 3-monthly in the HKEH Glaucoma Clinic, with documentation of bilateral IOP. IOP is measured with a Goldmann applanation tonometer on a slit-lamp biomicroscope. The reading in mm Hg is rounded to the next higher integer. Each measurement is repeated, and if the two readings differ by 3 mm Hg or more, a third measurement is taken. The median of the two or three measurements becomes the

IOP determination.

Documentation of disease progression

All recruited PACG patients will attend 6-monthly study visits. Although patients may be seen between study visits, data from these examinations were not routinely collected. Examinations and investigations at each study visit will include:

1. Documentation of optic nerve head appearance, in particular the vertical cup-to-disc ratio (VCDR)
2. Automated perimetry using the Humphrey Field Analyzer II (Carl Zeiss Meditec, Dublin, California, USA) (central 24-2 threshold test, Sita standard strategy, size III white stimulus, with the foveal threshold test turned on)
3. Retinal nerve fiber layer thickness measurement by Optical Coherence Tomography III (OCT III) imaging system (Stratus OCT, Carl Zeiss Meditec, Dublin, California, USA)

All these examinations and investigations are non-invasive, and are standard follow-up routines for all glaucoma patients. Participation in this study would require performance of visual field examination and retinal nerve fiber layer thickness scan at slightly higher frequency than normally required for clinical management. In routine clinical management, such investigations are usually performed at least once a year, and often more frequently in advanced or unstable patients. Performing these investigations more frequently may allow earlier detection and confirmation of glaucomatous progression.

Three strategies will be employed to detect disease progression:

1. Structural assessment - Retinal nerve fiber layer thickness measurement by Optical Coherence Tomography III (OCT III) imaging system (Stratus OCT, Carl Zeiss Meditec, Dublin, California, USA)

The GPA™ Advanced Serial Analysis software (Advanced Analysis Package of Stratus OCT™ Software Version 5.0) in the Stratus OCT will be used to quantify the progressive thinning of the retinal nerve fiber layer thickness, and also for analysis of statistical significance. The outcome measure is the mean decrease in retinal nerve fiber layer thickness per year, over the 3-year study period.

1. Functional assessment 1 – Automated perimetry using the Humphrey Field Analyzer II (Carl Zeiss Meditec, Dublin, California, USA) (central 24-2 threshold test, Sita standard strategy) with **Visual Field Defect Scoring (VFDS)**9

Visual Field Defect Scoring (VFDS), as defined and used in the Advanced Glaucoma Intervention Study (AGIS)9 for POAG, will be used to score Humphrey Field Analyzer II (Carl Zeiss Meditec, Dublin, California, USA) printouts (central 24-2 threstold test, Sita standard strategy, size III white stimulus, with the foveal threshold test turned on). VFDS range from 0 (no defect) to 20 (end-stage). If an eye has insufficient vision for a patient to count fingers at 30 cm, the visual field defect score is recorded as 20.The method of analysis used in AGIS6 will be repeated to compare the correlations between IOP and disease progression in POAG and PACG. The outcome measure is change from baseline in follow-up VFDS (range, 0 to 20 units).

1. Functional assessment 2 – Automated perimetry using the Humphrey Field Analyzer II (Carl Zeiss Meditec, Dublin, California, USA) (central 24-2 threshold test, Sita standard strategy) with **Guided Progression Analysis (GPA™) software** (Carl Zeiss Meditec, Dublin, California, USA)

The Humphrey Guided Progression Analysis (GPA™) software in the Humphrey Field Analyzer II (Carl Zeiss Meditec, Dublin, California, USA) is derived from the analysis used in the EMGT study.10 The GPA software uses the pattern deviation plot, point-by-point, to detect progression. It will be used in this study to quantify the progressive deterioration in visual field / retinal sensitivity to light, and also for analysis of statistical significance. The outcome measure is the mean decrease in mean deviation (MD) per year, over the 3-year study period.

**(d)** **Sample size calculation**

We aim for a sample size of 500 treated PACG patients. To cover the loss of subjects who have withdrawn from the study, the planned sample size currently would be 575 subjects, including 44 subjects from our ongoing study titled ‘*To determine the role of vascular changes in optic nerve head, retina, and choroid, in the pathogenesis of glaucoma’* (Ref.: KC/KE-17-0099/ER-3) who had provided informed consent for this study.

There is no published preliminary data for proper sample size calculation. This sample size is achievable, taking into consideration the patient volume of our hospital. For reference, AGIS (the study that established the correlation between IOP and disease progression in POAG) recruited 738 patients.

**(e)** **Results analysis**

The primary objective of this study is to examine the relationship between clinic IOP during follow-up and glaucoma progression, as defined by the 3 strategies above. Adapted versions of the two analyses described and used in the AGIS study will be employed to address this objective.6

The first, designated **Predictive Analysis**, is designed to assess whether IOP during early follow-up is predictive of subsequent change from baseline in the 3 outcome measures described above. Each eye is assigned to one of three categories in accordance with its IOP averaged over the 6-month, 12-month, and 18-month visits: less than 14 mm Hg, 14 to 17.5 mm Hg, and greater than 17.5 mm Hg. Then, for each subsequent 6-month follow-up visit, the mean change from baseline in the 3 outcome measures described above is calculated for each of the three IOP groups.

In the second analysis, designated **Associative Analysis**, the percent of visits over the first 3 years of follow-up for which an eye presented with IOP less than 18 mm Hg was determined. In accordance with this percent, each eye was assigned to one of four categories: 100% (group A); 75% to less than 100% (group B); 50% to less than 75% (group C); and 0% to less than 50% (group D). Then, for each group and for each visit starting with the 6-month visit, the mean changes from baseline in the 3 outcome measures are calculated.

**(f)** **Statistical analysis**

SPSS 15.0 platform (SPSS Inc., Chicago, IL) will be used for statistical analysis.

Continuous variables are expressed as mean (± standard deviation), categorical variables as individual counts and proportions. Univariate analyses are performed using Wilcoxon signed-rank test as appropriate. We used P < 0.05 as the critical value to determine statistical significance.

In the AGIS study, the generalized estimating equations method of Liang and Zeger was used in both the Predictive and Associative analyses to estimate and test the association between

IOP and change in visual field defect score.6 As we are using only one eye from each study subject, we will not employ the generalized estimating equations method of Liang and Zeger in our analysis. Instead, we will use the Jonckheere-Terpstra test11 as our groupings can be ordered.

In the Predictive Analysis, Pearson correlation coefficients will be calculated between average IOP over the first three 6-month visits and 1) IOP at baseline, 2) IOP at subsequent visits, and 3) change from baseline in our 3 outcome measures at subsequent visits.

We will further adjust the visual field parameters for the presumed effect of cataract, as per the AGIS.12 This is accomplished by first estimating the expected change in visual field parameters from before to after cataract surgery. Then for eyes with cataract not yet removed, we use the estimates of expected change to remove analytically the presumed effect of cataract on visual field parameters when cataract is present.12

**(g) Patients’ privacy and rights**

All the clinical results generated from examinations and investigations in this study will be duplicated into 2 identical sets. One set, in printed hardcopy format, will be kept in the patients’ Hospital Authority medical records to facilitate clinical management of PACG. The other set, in both electronic and hardcopy formats, will be filed securely in the Clinical Research Offices of the Department of Ophthalmology & Visual Sciences at Hong Kong Eye Hospital and Prince of Wales Hospital. Electronic data will be kept in password-protected files and computers in rooms with restricted access. Hardcopies of investigation results will be filed in locked cabinets in rooms with restricted access.

Patients can request to withdraw themselves from this study at any time. In the event of patient withdrawal, all clinical data of that particular patient will be deleted and eliminated from the files of the Clinical Research Office. The clinical data in the medical records will, however, be retained for future clinical management.

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