RESEARCH STUDY PROTOCOL

Protocol Title:	A randomized clinical trial comparing phacoemulsification and goniosynechialysis with phacoemulsification alone in the management of primary angle closure
Protocol Number :	R796/80/2010
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Principal Investigator's Experience

- **Academic qualifications**

  MBBS 1995 University College, London, UK
  MRCOphth 2001 Royal College of Ophthalmologists, London, UK
  FRCOphth 2009 Royal College of Ophthalmologists, London, UK
  MD (Res) Clinical Research (University of London)

- **Clinical experience**

  Glaucoma fellowship at St Thomas' Hospital, London, UK. Several years clinical experience as a Higher Surgical trainee in UK. Over 100 glaucoma surgical procedures performed and over 1000 cataract procedures.

- **Research interests**

  My research interests lie in the field of glaucoma and specifically in the surgical management of glaucoma. To this end I have completed more than 2 years of clinical research, running a comparative trial of unaugmented and 5-Flurouracil augmented trabeculectomy in an East Asian population (**The Singapore 5-Fluorouracil trabeculectomy study**). This was conducted from 2002 to 2004 at Singapore National Eye Centre – during this time I was an employee of the Institute of Ophthalmology, London, UK. For this research I have been awarded the degree of MD (Res) Clinical Research by University of London, UK-. Much of my thesis was concerned with how to improve surgical outcomes in glaucoma patients and the long-term consequences of any such surgical interventions.

Study Background

Glaucoma is the worlds' leading cause of irreversible blindness with nearly 7 million bilaterally blind due to the disease, by some estimates, and as such, represents a disease with significant associated morbidity.[1] Furthermore, as glaucoma is primarily a disease of old age, as the number of elderly people in the world continues to rise, the number of people with glaucoma blindness is likely to have increasing economic burden and public health costs.
Primary glaucoma is classified into 2 types, Primary Open Angle Glaucoma (POAG) and Primary Angle Closure Glaucoma (PACG). Classification depends on configuration of the anterior chamber drainage angle, specifically if it is open or if it shows evidence of closure. The proportions of people with POAG and PACG are approximately equal, with the latter disease more common in Asians and women.[2] Although the result of both diseases is progressive cupping of the optic disc with corresponding visual fields loss, the mechanism by which this occurs is thought to be quite different in the two diseases. In POAG the mechanism is still to be established but in PACG it is thought that apposition of the peripheral iris to the drainage angle results in damage to the trabecular meshwork (TM) and the formation of peripheral anterior synaechiae (PAS) which act as a mechanical obstruction of aqueous outflow via the trabecular meshwork. This in turn results in raised intraocular pressure (IOP) and subsequent optic nerve damage. Apposition can occur in anatomically predisposed eyes, although a physiological dynamic element is likely to be involved also. Areas of the TM not obstructed by PAS are likely to retain some function, although it is not clear if this is at

the same level as in normal subjects. The functioning of the TM posterior to the areas of PAS has also yet to be established and it is hope that this study will help to elucidate this matter.

Conventional initial management of PACG is to perform laser peripheral iridotomy (LPI) to allow flow of aqueous from the posterior chamber to the anterior chamber through the iatrogenically created iridotomy. This has two benefits – in those subjects where pupillary-block is thought to be the mechanism for angle closure, it can reduce the risks of an acute rise in IOP occurring (acute angle closure). In other subjects with PAC, LPI has been shown to increase the drainage angle and this has led to lowering of the IOP in some subjects. However, in a retrospective review of 65 subjects with PACG who had had LPI, after 5 years follow-up the vast majority required further interventions (medications and/or surgery) to lower the IOP.[3] Furthermore, PAS formation has been show to still occur in the presence of a patent PI.[4] Clearly, the current conventional management strategy for PAC/PACG is inadequate and likely to lead to further ocular morbidity.

The poor results of LPI in the long-term for subjects with PACG in terms of IOP control has led many clinicians to study the effect of cataract surgery on IOP control in these patients. It was thought that removing the lens would increase anterior chamber depth and increase the drainage angle and hence increase outflow. Cataract surgery does indeed seem to open the drainage angle and its effects on IOP control have been promising.[5-8] However, opening of the drainage angle may be limited in subjects with significant PAS. This could compromise the IOP lowering effect of cataract surgery in this group of patients. In such cases, cataract surgery with mechanical breaking of PAS (i.e. goniosynechialysis) might lower IOP to a greater extent than cataract surgery alone. Phacoemulsification + intraocular lens + Goniosynechialysis (PEI-GSL) has been carried out in several published studies, with all studies reporting a reduction in post-operative IOP compared to pre-operative.[9-11] The main complications associated with PEI-GSL are excessive post-operative anterior chamber fibrinous reaction and anterior chamber bleeding. Theoretically, excessive pressure to break PAS could also cause irido- or cyclo- dialysis, with resultant ocular hypotony. In an effort to reduce these complication risks, Varma and Fraser described phacoemulsification + intraocular lens + viscogonioplasty (PEI-VGP) in which a viscoelastic is used to break PAS in a non-iris contact method, rather than using an instrument to push the iris back.[12;13] The authors proposed that this procedure would reduce the complications of PEI-GSL but still open the angle sufficiently. It is not clear however, if PEI-VGP would provide sufficient force to open areas of PAS and therefore be as efficacious as PEI-GSL in lowering IOP. Furthermore, there is no evidence that either PEI-GSL or PEI-VGP are superior to phacoemulsification + intraocular lens (PEI) alone in reducing IOP. Most surgeons will perform cataract surgery in patients with PAC/PACG and uncontrolled IOP. By adding the relatively simple step of goniosynechialysis during the surgical procedure, it has been proposed that this will result in further IOP lowering and hence less risk of glaucoma development/progression. This has yet to be proven.

An alternative treatment modality in subjects with PAC/PACG, visually significant cataract and high IOP, would be to perform phaco-trabeculectomy. Two recent randomized controlled trials published by Tham and co-workers, compared PEI versus phaco-IOL-trabeculectomy in subjects with medically controlled and medically uncontrolled angle-closure glaucoma. For the medically controlled group, there was no clinically significant difference in IOP lowering effect between the two surgical modalities.[14] For the medically uncontrolled group, both modalities reduced IOP but the phaco-IOL-trabeculectomy group had a significantly lower IOP.[15] However, the phaco-IOL-trabeculectomy group in both studies had a significantly higher complication rate than did the PEI group. Furthermore, only 4/27 (14.8%) of eyes in the PEI group (in the medically uncontrolled IOP study) required subsequent trabeculectomy to control IOP over the 2 years follow up period. In all these 4 cases, trabeculectomy was carried out successfully. Extrapolating from these data it would appear that although phaco-trabeculectomy does lower IOP more than PEI in patients with medically uncontrolled angle-closure glaucoma, many of these patients would not require 2 combined simultaneous procedures. Furthermore, trabeculectomy surgery has significant complication rates, even many years after the surgery is performed. Performing either PEI, or PEI-GSL (with or without viscoelastic assistance) would likely result in a significant reduction in IOP and still leave open the option of trabeculectomy (or glaucoma drainage device surgery) later on as the conjunctiva and sclera would be untouched. This multicentre study is designed to determine which of these 2 surgical options would superior in terms of efficacy and complications.

There have been no randomized controlled trials comparing PEI versus PEI-GSL (or PEI-VGP). There have been several case series and these will be summarized below.

Effect of phacoemulsification + intraocular lens on intraocular pressure in subjects with primary angle closure

In patients with PAC or PACG, there is considerable evidence that PEI lowers IOP. Hayashi and coworkers, in a prospective study of 77 eyes of 77 consecutive patient with PACG found that IOP decreased significantly from baseline by an average of 6.1 ± 3.9 mmHg at 1 year follow up.[5] Tham and co-workers showed an even more considerable decrease in IOP from a pre-operative mean of 24.4 mmHg to a mean of 15.4 mmHg at 15 months in a cohort of 27 patients with medically uncontrolled PACG.[13] The same group examined the effect of PEI in a cohort of 35 eyes with medically controlled PACG.[14] Pooling the results from both studies, PEI significantly reduced IOP from a pre-operative mean of 20.4 ± 5.8 mmHg to a mean of 14.6 ± 2.9 mmHg at 1 year, irrespective of pre-operative IOP control.[8]

Effect of phacoemulsification + intraocular lens + goniosynechialysis on intraocular pressure in subjects with primary angle closure

The largest case series on this topic, and the only prospective study performed on PEI-GSL was that performed by Teekhasaenee and coworkers.[9] Fifty-two eyes of 48 patients (from Thailand) with PACG all underwent laser peripheral iridotomy but continued to have raised IOP defined as IOP >21 mmHg. Subjects underwent PEI-GSL and IOP decreased from a pre-operative mean of 29.7 ± 7.9 mmHg to 13.2 ± 2.9 mmHg at final examination (mean follow up 20.8 ± 15.5 months, range 5-76 months). This is a mean decrease of 16.5 mmHg.

There are 2 studies on the effect of PEI-VGP on IOP control, both retrospective case series. In the first, a consecutive series of 15 eyes of patients with refractory PACG, PEI-VGP reduced IOP significantly from 27.4 mmHg (on medication) to 14.1 mmHg (off all medication in 14/15 eyes), at 6 months.[13] This represents a decrease of 13.3 mmHg. A subsequent study of 11 patients (11 eyes) on subjects with PACG (all of whom had refractory control despite patent peripheral iridotomy) showed a decrease in IOP from 39.4 mmHg pre-operatively to a mean of 13.4 mmHg after PEI-VGP at 7.8 months follow up.[16]

Effect of phacoemulsification + intraocular lens alone or phacoemulsification + intraocular lens + goniosynechialysis on angle opening in subjects with primary angle closure

There are several studies which have shown that the drainage angle opens significantly after PEI in subjects with PAC/G.[17;18] Only one paper described the effects of PEI on extent of peripheral anterior synaechiae. This showed that in subjects with PACG and PAS, there was a significant reduction in the extent of PAS after PEI, by approximately 25%.[8]

Most studies of PEI-GSL also describe opening of the drainage angle in subjects with PAC/G. Several studies also describe reduction in extent of PAS, including complete elimination of PAS.[9;11;13;19-22]

The population to be studied will be all patients attending SNEC, TTSH, NUHS, Vietnam National Institute of Ophthalmology, Thailand Faculty of Medicine Siriraj Hospital, Mahidol University and Hongkong, Queen Mary Hospital

This study will be conducted in compliance with the protocol, SGCP and the applicable regulatory requirement(s).

Study Objectives and Purpose

To evaluate and compare the effect of two different surgical interventions in patients with primary angle-closure (with or without glaucoma), high intraocular pressure, and cataract.
These interventions are:
(a) phacoemulsification + intraocular lens (PEI)
(b) phacoemulsification + intraocular lens + goniosynechialysis (PEI-GSL).

Study Design

Experimental design
This is prospective, longitudinal multicentre randomized control trial. The study sites will be SNEC, TTSH, NUHS, Vietnam National Institute of Ophthalmology, Thailand Faculty of Medicine Siriraj Hospital, Mahidol University and Hongkong, Queen Mary Hospital
All subjects will undergo baseline and subsequent follow-up and evaluation in a standardized manner. Those who complete the informed consent process and the baseline examination will be randomized to undergo either treatment with PEI or PEI-GSL. The investigators measuring the main outcome measures will be masked to the treatment. Subjects will then be followed-up for 12 months.

Study hypothesis
We hypothesize that, compared to PEI, PEI-GSL will result in significantly lower IOP reduction both in the short and long term, with a reduction in amount of PAS, a wider drainage angle and a similar complication rate as PEI.

Patient Selection
All subjects attending the glaucoma clinic at SNEC, TTSH, NUHS, Vietnam National Institute of Ophthalmology,Thailand Faculty of Medicine Siriraj Hospital, Mahidol University and Hongkong, Queen Mary Hospital will be eligible to be included in the study if they fulfill the inclusion/exclusion criteria (see below).

Once these criteria are fulfilled, subjects will be enrolled and divided into 2 groups using a random number generator. Group 1 will undergo PEI alone and Group 2 will undergo PEI-GSL

Randomization and masking
Following consent the study coordinator will contact the study centre (SERI) to obtain the randomization for each enrolled patient. Randomization will be of patients and not eyes i.e. if two eyes of the same patient are eligible they will undergo the same intervention as allocated. All personnel performing study procedures, notably the main outcomes of IOP, visual fields and optic disc assessment and photography, will be masked to the randomization of patients. The masking code will be held by SERI and the code will be broken only after the study has been completed and analysis has taken place.

Surgical technique
Anaesthetic will be general or peribulbar (approx. 3ml volume of 50/50 mix of 2% lignocaine and Marcaine with hyaluronidase). A superior or temporal clear corneal incision will be performed followed by creation of a paracentesis, injection of 3% sodium hyaluronate, 4% chondroitin sulfate (Viscoat, Alcon laboratories) and capsulorhexis. Hydrodissection is then performed using balanced salt solution and the lens is removed using phacoemulsification of the lens nucleus and aspiration (automated or manual) of cortical lens matter. After further injection of Viscoat, an acrylic injectable intraocular lens will be inserted into the capsular bag, its power having been determined pre-operatively based on biometric measurements. The Viscoat will then be removed (automated or manual), in the case of subjects undergoing PEI.
For those subjects PEI-GSL, the goniosynechialysis will be performed after partially filling the anterior segment with Sodium Hyaluronate 14mg/ml (Healon GV, Advanced Medical Optics (AMO), California, USA). Using a Gonio lens (with coupling agent) to visualize those areas of PAS (defined pre-operatively), the viscoelastic will be used to break areas of PAS wherever possible, without touching the TM or iris. In cases where the viscoelastic is unable to break PAS, an iris repositor will be used to gently break the PAS in the areas where it exists. After this is performed, the surgery will continue as above, with removal of any remaining viscoelastic by automated or manual irrigation and aspiration. Surgeries will be performed by senior ophthalmic surgeons. Any intraoperative complications (such as posterior capsular rupture, hyphaema, iris damage) will be recorded.

Outcome measures

Primary

1. Intraocular pressure at 12 months

Secondary

1. Intra- or post operative complications
2. PAS development (at 12 months)
3. Degree of angle opening as measured by gonioscopy and AS-OCT

Examination methods

INTRAOCULAR PRESSURE (IOP): The protocol for measuring IOP will follow the same guidelines used in the Collaborative Initial Glaucoma Treatment Study (CIGTS).[23] IOP will be measured using a Goldmann applanation tonometer (Haag-Streit, Switzerland) after administration of a single drop of topical anaesthetic (amethocaine hydrochloride 0.5%) into the inferior conjunctival sac, and staining of the tear film with a dry strip of fluorescein. Two IOP measurements will be recorded, and unless they vary by more than 2 mm Hg, the average will become the final IOP value for data entry. A third measurement will be taken if the first 2 varied by more than 2 mm Hg, and the median of the 3 will then be used as the IOP value of record. The calibration of tonometers will be checked monthly.

VISUAL FIELDS (VF): The VF assessment will follow the same protocol as the Early Manifest Glaucoma Trial (EMGT) except the strategy.[24] Humphrey 24–2 full threshold fields will be used for baseline and follow-up testing. If the visual field examination has been done within six months of the baseline visit and it is reliable, then it may be used for the baseline visit.

OPTIC DISC: Optic disc will be evaluated by standardized and independently determined criteria. Assessment will be based on photographic criteria and HRT disc topography (see below). These criteria require clear change on an optic disc follow-up photograph or HRT image, and confirmed by side-by-side grading in 2 consecutive visits.

DISTANCE VISUAL ACUITY: Monocular visual acuity (VA) will be assessed with and without correction using a LogMAR chart under standard lighting. Subjective refraction will be performed using a modified version of the Early Treatment of Diabetic Retinopathy Study Protocol (EDTRS) and subsequent best-corrected VA will be measured.

HEIDELBERG RETINAL TOMOGRAPHY: The HRT is a scanning laser ophthalmoscope used to image the optic disc. Global and segmental disc and cup areas are analyzed directly by means of HRT software using the standard reference plane.

CORNEAL SPECULAR MICROSCOPY: Non-contact specular microscopy will be performed at the central and peripheral regions of the cornea using TOPCON SP-2000P. This method measures the state of the corneal endothelium; the parameters to be determined are endothelial cell density, cell area, coefficient of variation (CV) in cell area and hexagonality.

DISC PHOTOGRAPHY: Digital stereo photographs through dilated pupils will be taken for each patient at baseline and 12 months.

SLIT LAMP BIOMICROSCOPY will be performed without dilation of the pupil and will assess the conjunctiva, cornea, anterior chamber, lens, anterior vitreous and iris/pupil using a Haag-Streit slit lamp.

GONIOSCOPY will be performed to assess the anterior chamber angle at baseline, 6 months and 12 months. Static and dynamic gonioscopy will be performed at baseline by a single observer who will be a trained ophthalmologist. Under the lowest level of ambient illumination that permits a view of the angle and at high magnification (x 16 to x 25), the drainage angle will be graded according to Shaffer's convention in each quadrant. Dynamic indentation gonioscopy using a Sussman or Zeiss lens will be used to detect peripheral anterior synechiae (PAS).

ANTERIOR SEGMENT OCULAR COHERENCE TOMOGRAPHY (AS-OCT). All subjects will undergo imaging of the angle before surgery and at 12 months after surgery using the AS-OCT (Carl Zeiss Meditec, Dublin, CA). Standardized angle parameters will be calculated after manual identification of the scleral spur (SS). The angle opening distance at 500 µm (AOD_{500}) anterior to the SS and a modification of the angle recess area, the trabecular-iris surface area at 750 µm ($TISA_{750}$) anterior to the SS will be measured. The SS is determined as the point where there is a change in curvature of the inner surface of the angle wall, often appearing as an inward protrusion of the sclera.

Treatment modification protocol

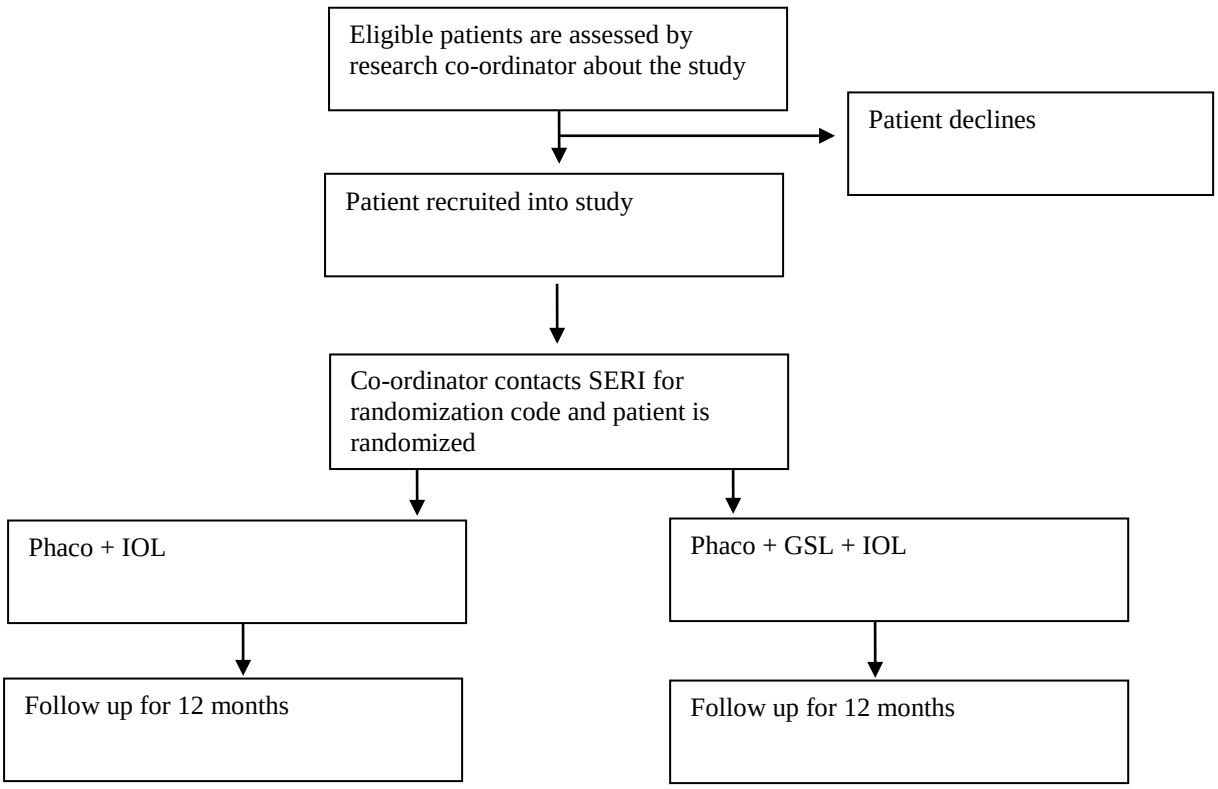
The intervention protocol will require that medication be initiated or changed whenever any of the following criteria are present:

1. Inadequate reduction of IOP as confirmed by two consecutive IOP measurements (1 to 14 days apart), treatment failure defined as IOP >21 mmHg, excluding first postoperative week.
2. Deterioration of a visual field (confirmed with another VF test within 14 days).
3. Optic disc deterioration, relative to the reference time, as assessed subjectively by fundoscopy and objectively by evaluation of disc stereo photographs.
4. Adverse signs or symptoms severe enough to warrant a change in medication.

Trial related examination procedures and tests

Examination	Screening	Baseline	Day 1	Day 5	4 weeks	3 months	6 months	12 months Exit
Counselling/ Informed consent	√							
Visual acuity	√	√	√	√	√	√	√	√
Subjective refraction		√			√			√
HVF		√						√
HRT		√						√
Endothelial Cell Count		√						√
Slit lamp biomicroscopy	√	√	√	√	√	√	√	√
IOP†	√	√	√	√	√	√	√	√
Gonioscopy	√	√					√	√
Disc photo††		√						√
Central corneal thickness		√						√
Anterior segment OCT		√						√

Patient flow



Study Timeline

Study Timeline			
TRIAL ACTIVITY		Date	
		From	To
Study Initiation	Plan	Jan 2011	
	Actual		
Recruitment	Plan	Jan 2011	Jan 2012
	Actual		
Follow-up Visits	Plan	Jan 2011	Jan 2013
	Actual		
Interim analysis (if applicable)	Plan		
	Actual		
Study Closure	Plan	Jan 2012	Jan 2013
	Actual		
Final report	Plan	Jan 2013	
	Actual		

*: To amend as per study requirement

Selection and Withdrawal of Subjects

Inclusion criteria

1. Age ≥ 30 years
2. Diagnosis of PAC or PACG. PAC is defined as previous documentation that the posterior trabecular meshwork was not visible for 180 degrees or more with gonioscopy (without indentation) previous to any LPI having been performed and evidence of appositional closure of the drainage angle by the peripheral iris, such as iris pigment in the angle or PAS, or any record of IOP > 21mmhg. PACG is defined as PAC as above and in addition glaucomatous optic neuropathy. Glaucomatous optic neuropathy is defined as functional and structural evidence of glaucomatous damage consistent with cup-disc ratio $\geq$ 0.7 or asymmetry $\geq$ 0.2 between eyes or a neuroretinal rim width $\leq$ 0.1 CDR (at 11-10 or 5-7 0' clock). Glaucomatous field defect is diagnosed with reliable threshold visual field examination of the central 24° using SITA-STD 24-2 strategy, with glaucoma hemifield test results being outside normal limits, and with three or more non-edge contiguous points (except the horizontal nasal meridian) depressed to P<5%
3. IOP >21 mmHg or ≤ 21 mmHg on topical medication
4. More than or equal to 90 degrees of PAS (not necessarily contiguous)
5. Lens opacity deemed sufficient to be causing decreased vision in the opinion of the operating surgeon.
6. Informed consent

Exclusion criteria

1. Previous intraocular surgery (laser iridotomy is allowed)
2. Previous eye trauma resulting in documented damage to the drainage angle (such as angle recession)
3. For patients on warfarin, INR >3.0 on day of surgery
4. Evidence of moderate non-proliferative diabetic retinopathy, neovascularization, or rubeosis iridis
5. Chronic use of topical or systemic steroids
6. Any condition precluding or presumed to preclude reliable visual fields, disc stereo photography, or 12 months of follow up
7. Only eye (VA worse than 6/60 Snellen in non-study eye)
8. Advanced glaucoma with severe paracentral or generalized field deficit threatening fixation
9. Allergic to acetozolamide

Subjects who withdraw will not be replaced. They will be followed up as normal in the glaucoma clinic. Data from the nearest follow up visit to 12 months will be analysed at the conclusion of the study.

Treatment of subjects

All subjects, regardless of which study arm they are in, will or may receive the following postoperative medications, unless there are contraindications (such as allergies):

1. Prednisolone 1% for at least 3 days
2. Antibiotic drops for 1 month
3. PO Acetazolamide as necessary
4. PO Potassium 600mg as necessary

Compliance will be checked verbally at each clinic visit

The intervention protocol will require that medication be initiated or changed whenever any of the following criteria are present:
1. Inadequate reduction of IOP as confirmed by two consecutive IOP measurements (1 to 14 days apart), treatment failure defined as IOP >21 mmHg, excluding first postoperative week.
2. Deterioration of a visual field (confirmed with another VF test within 14 days).
3. Optic disc deterioration, relative to the reference time, as assessed subjectively by fundoscopy and objectively by evaluation of disc stereo photographs.
4. Adverse signs or symptoms severe enough to warrant a change in medication.

Assessment of efficacy

Efficacy will be determined by IOP measurements (Goldmann applanation tonometry) at regular intervals as defined above. All IOP measurements will be recorded in the case report forms

Assessment of safety

A list of intraoperative, early (within 1 month of surgery) and late (after 1 month) will be obtained from the 'Guidelines on design and reporting of glaucoma surgical trials' document published in 2009 by the World Glaucoma Association. The list of potential complications is too exhaustive to list here but all the measures will be specifically examined for at the appropriate post operative clinic visit.

All complications will be recorded in the case report forms and any patients having a complication or adverse event will be followed up for as long as is clinically necessary.

Statistics

To determine the effects of the surgery on intraocular pressure a comparison will be made of the change from pre-surgery to post-surgery of each of the measurements. The change from baseline will be compared within the groups using a paired t-test if the differences are determined to be normally distributed. If the differences are non-normal a Wilcoxon signed-rank test will be completed. To compare the two treatment groups, unpaired t-tests will be used in the case of normally distributed data; otherwise Mann-Whitney U test will be used. The level of significance will be 0.05 for a two-sided test. Patients data will be analysed on an intent-to-treat basis.
Sample size calculations
Based on previously published studies, the difference in IOP between the 2 groups at 1 year was 7.5 mmHg.[9;15] Taking a conservative estimate of a difference of 4mmHg, and a standard deviation from the above studies' sample populations of 5.5 mmHg, 35 subjects would be needed in each arm for the study to have an 88% power to detect a difference between the null (no difference in mean IOPs postoperatively) and alternate (4 mmHg difference between the 2 postoperative means) hypotheses at the 0.05 significance (alpha) level. Assuming a drop out rate of 10%, 78 subjects would be needed to be recruited into this study.

An independent data monitoring company will be used to input the data. Any missing data will be obtained from the original case notes and any spurious data identified will be similarly checked.

Safety and adverse events

Adverse Event
An **adverse event** is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Serious Adverse Event
A **serious adverse event** is any untoward medical occurrence at any dose that:

- Results in death or;
- Is life-threatening or;
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event:

Reporting of Adverse Events

1) Notification to EC/IRB

a. Local SAEs refer to SAEs occurring at any site within SingHealth. **Local SAEs (expected and unexpected)** that result in death, regardless of causality, should be reported to the IRB and CMB of the institution by meeting, telephone, fax or email within 24 hours of the PI becoming aware of the event. This should be followed by a full report using the SAE Reporting Form within 7 calendar days.
b. **Local unexpected/expected SAEs** that are **definitely/probably/ possibly related events** and are **life-threatening**, should be reported to the IRB as soon as possible but not later than 7 calendar days after the investigator is aware of the event, followed by a complete report within 8 additional calendar days.
c. **Local unexpected SAEs** that are **definitely/probably/ possibly related events**, but **not life-threate**ning, should be reported as soon as possible but not later than 15 calendar days after the investigator is aware of the event.
d. An **increase** in the **rate of occurrence** of **local expected SAEs**, which is judged to be clinically important, should be reported within 15 calendar days after the PI is aware of the event.
e. Local expected SAEs that occur at the rate anticipated in the initial study proposal should be reported at least annually (when submitting the annual report) using the AE summary form
f. Non-local SAEs refers to SAEs occurring at any site outside SingHealth. **Non-local unexpected SAEs** that are **definitely/probably/ possibly related events**, and **are fatal or life-threatening** should be reported as soon as possible but not later than 30 calendar days after the PI is aware of the event.
g. **Expected and unexpected local AEs** that are **definitely/probably/ possibly related events** should be reported at least annually (when submitting the annual report).

2) Notification to HSA

All **SAEs** that are **unexpected** and **related to the study drug** will be reported to HSA:

a. The investigator is responsible for informing HSA no later than 5 calendar days after first knowledge that the case qualifies for expedited reporting. Follow-information will be actively sought and submitted as it becomes available.
b. The Investigator shall notify HSA by telephone or by facsimile transmission of any **unexpected fatal** or **life-threatening SAE associated with the use of the drug** as soon as possible but no later than 7 calendar days after first knowledge that a case qualifies, followed by a complete report within 8 additional calendar days.

Direct Access to Source Data

The Investigator(s)/ Singapore National Eye Centre will permit study-related monitoring audits, MCRC and or EC review and regulatory inspection(s), providing direct access to source data/ document.

Quality Control and Quality Assurance

- to include if applicable

Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Singapore Good Clinical Practice and the applicable regulatory requirements.

The final study protocol, including the final version of the Patient Information and Informed Consent Form, must be approved or given a favorable opinion in writing by the Centralised Institutional Review Board and regulatory approval from the Health Sciences Authority, HSA (regulatory approval only applicable for drug-related clinical trials), prior to the enrolment of any patient into the study.

The Principal Investigator is responsible for informing the Centralised Institutional Review Board and HSA (where applicable) of any amendments to the protocol or other study-related documents, as per local requirement.

Data Handling and Record Keeping

A data management service will be used for this purpose. Data will be destroyed after 15years.

Funding and Insurance

- Information on funding and insurance if not addressed in a separate agreement

References

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