BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032957
Article Type:	Protocol
Date Submitted by the Author:	14-Jul-2019
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Keywords:	Primary congenital glaucoma, Trabeculotomy, PCG, Combined trabeculotomy-trabeculectomy, Randomized controlled trial

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Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for Primary Congenital Glaucoma: Study Protocol of a Randomized Controlled Trial

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Word count: 3569

Abstract

Introduction: Trabeculotomy and combined trabeculotomy-trabeculectomy (CTT) are major surgical options for primary congenital glaucoma (PCG). However, it is unclear which of the two surgical procedures should be recommended as the optimum first-line treatment for PCG. This trial aims to determine whether the surgical outcomes of trabeculotomy is not inferior to that of CTT for PCG with a horizontal corneal diameter (HCD) of 12-14 mm.

Methods and analysis: This is a 3-year, noninferiority, prospective, randomized controlled trial. We anticipate recruiting 248 participants (aged ≤ 3 years) with PCG with an HCD of 12-14 mm, from the Department of Glaucoma, Zhongshan Ophthalmic Center, Guangzhou, China. One eye per participant will be randomly (1:1) assigned to receive trabeculotomy or CTT. The primary outcome is the 3-year postoperative success rate, and the secondary clinical outcomes will include visual acuity (VA), HCD, corneal thickness, axial length, cup-disc ratio, refractive error, and postoperative complications. Data will be analysed by the intention-to-treat principle.

Ethical approval and dissemination: The study protocol has been approved by the ethics committee of Zhongshan Ophthalmic Center (2014MEKY023) and the "5010 Plan" evaluation committee at Sun Yat-Sen University, Guangzhou, China. The results will be disseminated in international academic meetings and published in peer-reviewed journals.

Trial registration: Chinese Clinical Trial Registry, ChiCTR-IOR-14005588; Date registered: 20 November 2014.

Keywords: PCG, Primary congenital glaucoma, Trabeculotomy, Combined trabeculotomy-trabeculectomy, Randomized controlled trial

Article Summary

Strengths and limitations of this study

- The trial design is prospective, randomized and controlled with a relative large sample size, and the follow-up is comparatively long (3 years).
- To date, the study is the first randomized controlled trial that comprehensively evaluate the surgical and visual outcomes of trabeculotomy and CTT in treating PCG patients with an HCD of 12 to14 mm, and surgical complications.
- This study includes many important clinical measurements that use standardized protocols, such as HCD, axial length, corneal thickness, C/D ratio, refractive errors and VA. Importantly, structural changes can be observed dynamically in follow-up visits.
- This is a single-center trial, which may induce selection bias.
- Participants may drop out of the study during the long-term follow-up, which is a potential threat to external validity.

INTRODUCTION

Primary congenital glaucoma (PCG) is one of main causes of blindness in children. Liu *et al*[1] reported that congenital glaucoma accounts for 5.1% of all congenital ocular diseases in a Chinese population. It is estimated to accounts for 0.01–0.04% of blindness worldwide.[2] In India, the disease accounts for 4.2% of all childhood blindness.[2] Haddad *et al*[3] evaluated 3210 visually impaired children and found that, PCG was responsible for 10.2% of the visual impairments. Since at least 50% of eyes with PCG presenting at birth will become legally blind, patients with PCG require prompt treatment and follow-up examinations throughout their lives.[4]

Among all the treatment options, surgical intervention is the main treatment for PCG. Goniotomy and trabeculotomy have been considered initial procedures because of the high success rates.[5,6] However, goniotomy can be performed only if the cornea is clear, while trabeculotomy does not require a clear cornea. Trabeculotomy reduces intraocular pressure (IOP) by tearing the trabecular meshwork into the anterior chamber. Regarding complications, hyphema is more common with trabeculotomy but can resolve spontaneously and cause no additional problems.[7-9]

Combined trabeculotomy-trabeculectomy (CTT) has been advocated for treating moderate to severe congenital glaucoma.[10] The rationale for CTT is to gain access to the dual outflow, through Schlemm's canal and the

trabeculectomy fistula. The application of Mitomycin-C (MMC) can improve the surgical success rates of CTT,[11] which is, however, disputed by some other studies.[12,13] Complications after CTT surgery, such as hyphema, bleb-related infections, and choroidal detachment, have been reported.[14]

Although some studies have indicated that trabeculotomy and CTT are equally effective in lowering IOP,[7,9,15] their results were inconsistent with others.[10,16] There is a paucity of randomized controlled trial with large sample size comparing the results of trabeculotomy with CTT for PCG. A randomized trial by Khalil *et al*[9] which included a cohort of 28 eyes of 28 children younger than 2-year-old with mean follow-up time of 3 years concluded that both trabeculotomy and CTT with MMC had similar outcomes. However, due to limited sample sizes, it was still difficult to determine which procedure was more preferred.[17]

The horizontal corneal diameter (HCD) is usually increased in PCG patients, which indicates the disease severity and can be used as a rough guide for surgery selection.[18] In general, angle surgeries are recommended for PCG with an HCD <12 mm. Huang *et al*[8] described 21 eyes of 12 patients with a mean age of 26.1 days (range: 11 – 28 days) who underwent trabeculotomy with a mean follow-up period of 46.9 months (range 12–122 months). Their success rate was 100% regardless of the medications used. Trabeculectomy or CTT with or without the use of MMC is usually chosen for advanced cases with an HCD exceeding 14 mm, which is consistent with previous studies.[7,19]

However, which surgical procedure for PCG with HCD of 12-14 mm offers better outcomes and results in fewer complications remains unknown.

Study objectives

The primary aim of our study is to compare the 3-year success rate between trabeculotomy and CTT in patients with PCG with an HCD of 12-14 mm. The secondary aim is to assess the changes in biological parameters of eyeball, visual outcomes and postoperative complications of these two surgical procedures.

METHODS AND ANALYSIS

This protocol is developed in line with the Standard Protocol Items Recommendations for Interventional Trails (SPIRIT). The SPIRIT checklist for the protocol is available as 'supplement'. The trail was registered at Chinese Clinical Trail Registry (www. Chictr. org. cn) on 20, November 2014 with a number of ChiCTR-IOR-14005588. Version identifier 1.4 of this trial protocol was approved on 25 August 2014.

Trial design and setting

This study is a 3-year, prospective, randomized, single-center, noninferiority trial comparing two surgical procedures (trabeculotomy versus CTT) on the surgical and visual outcomes and postoperative complications in the treatment of PCG with an HCD 12- 14 mm. Eligible patients will be enrolled and randomly assigned to receive either trabeculotomy or CTT (figure 1). The trial is being

conducted at the Zhongshan Ophthalmic Center, Guangzhou, China.

Participant selection

Inclusion criteria

Participants will be included if they meet all of the following criteria: (1) diagnosis of PCG in either eye; (2) Under 3 years of age; (3) HCD between 12 and 14 mm; (4) no previous intraocular surgery or laser treatment.

PCG is defined as follows:

1. Age of onset ≤ 3 years old.
2. IOP >21 mmHg.
3. Absence of other ocular or systemic diseases.
4. Combined with one or more of the following clinical signs: (1) corneal findings: Haab's striae, corneal edema, corneal diameters >11 mm in the newborns, >12mm in children younger than 1 year old, and >13mm in children older than 1 year old;[20] (2) increased (>0.3) or asymmetric (>0.2) C/D ratio; and (3) abnormally increased axial length (AL). Normal AL is as follows: 3mo-3yrs: 19-22 mm.[21]

Only one eye per patient will be enrolled. If both eyes of a patient are eligible for the study, the eye with the higher base-line IOP will be selected. The treatment for the fellow eye will be determined at the physician's discretion.

Exclusion criteria

Patients will be excluded if they meet any of the following criteria:

- Inability of the patients' legal guardian to give informed consent.
- Inability of the patient to return to the clinic for the scheduled study visits.
- Contraindications to anesthesia or surgery for ocular disease.
- An HCD less than 12 mm or greater than 14 mm.
- Severe corneal cloudiness precluding anterior chamber visualization.
- Secondary congenital glaucoma.
- Prior intraocular surgery.
- Other coexisting ocular diseases such as an abnormal cornea, congenital iris abnormality, congenital cataract, or retinopathy of prematurity.

Withdrawal criteria

1. Failure to locate or dissect Schlemm's canal by 120°.
2. Presence of any of the following issues during the operation: severe anesthesia accident, suprachoroidal hemorrhage, vitreous loss, or a change in the operative procedure according to the patient's condition.
3. Desire to quit the trial.

The withdrawal criteria described above have been established to ensure that the outcomes of the two procedures (trabeculotomy and CTT) will be effectively analyzed for the full 3-year duration of the study.

Sample size calculation

The sample calculation is based on the hypothesis that the 3-year success rate of trabeculotomy will not be inferior to that of CTT. Published studies have showed that the success rate at the 3rd year after CTT ranged from 72.6% to 87%.[1,9,22,23] Success is defined as an IOP ≤ 21 mmHg with or without glaucoma medication, no requirement for additional glaucoma surgery and no evidence of progression or enlargement of the cup-disc ratio (C/D ratio) or HCD.[7,8] We assume that the 3-year success rate of CTT will be approximately 80%. In this trial, we expect no significant difference in the 3-year success rates between the two groups; therefore, a sample size of 224 will provide a power of 80% and a one-sided test at 2.5% significance. Assuming a 10% loss to follow-up, a sample size of 248 participants is required for this study, with 124 participants in each group.

Patient recruitment and baseline data collection

All subjects will first be assessed for potential participation in the study by the primary investigator. Patients identified as eligible for the study in the survey will be invited to undergo enrollment examinations to verify their eligibility for enrollment in the trial.

Examinations

IOP. IOP will be measured with a Tono-Pen Avia (Reichart, Depew, New York, USA) under sedation with chloral hydrate 10% and topical anesthesia.

Although anesthetic agents used during examination under anesthesia (EUA) may influence IOP and affect the accuracy of IOP documentation, chloral hydrate 10% has a minimal effect on IOP in pediatric ophthalmic examination.[18]

Slit-lamp examination. The condition of the anterior segment, including corneal clarity, corneal edema, Haab's striae, anterior chamber depth, iris, pupil, and lens, will be evaluated using a hand-held slit lamp (Keeler, Bucks, England).

Corneal clarity will be recorded as mild (iris texture clearly seen), moderate (iris seen but texture not clearly visible), and severe (iris not visible).

HCD. A caliper will be used to measure the HCD (white to white) by experienced ophthalmologists. Participants with an HCD less than 12 mm or greater than 14 mm will be excluded.

Corneal thickness. Corneal thickness will be measured using ultrasound pachymetry (IOPac, Heidelberg Engineering, Heidelberg, Germany).

C/D ratio. The C/D ratio will be evaluated using direct ophthalmoscopy (66 Vision, Suzhou, China) as permitted by the media clarity. Images showing of the C/D ratio will be obtained using a hand-held retinal camera (Kowanonmyd a-D III; KowaOptimedInc, Aichi, Japan) through a dilated a pupil. For children with hazy media, whose fundus cannot be visualized, B-scan ultrasound (Quantel Medical, CF, France) will be used to rule out any intraocular pathology and to detect excavation of the optic nerve head.

Ocular biometry. Ocular biometry, including AL, anterior chamber depth, lens thickness, and vitreous chamber depth, will be measured using A-scan ultrasound (Quantel Medical, CF, France). Ten repeated measurements will be taken and averaged for analysis.

Visual acuity (VA). VA will be measured using suitable procedures. Teller acuity cards (Vistech Consultants, Inc. Dayton, OH, USA) will be utilized at a distance of 55 cm for nonverbal children. The Lea symbols (Precision Vision, La Salle, IL) with a test distance of 3 meters and the Early Treatment of Diabetic Retinopathy Study (ETDRS) LogMAR E chart (Precision Vision, Villa Park, Illinois, USA) with a test distance of 4 meters will be employed for verbal children. Monocular VA will be assessed in the right eye followed by the left eye. For children who cannot complete the quantified VA examinations mentioned above, the ability to fix and follow light will be evaluated.

Refractive error. Refraction will be measured by retinoscopy after cycloplegia. Cycloplegia will be induced with two drops of cyclopentolate 1% instilled 5 min apart, with a third drop administered after 20 min. Cycloplegia will be then evaluated after an additional 15 min. Cycloplegia is considered complete if the pupil dilates to ≥ 6 mm and a light reflex is absent.[24]

All ophthalmological examinations described above will be performed in both eyes and under sedation using chloral hydrate 10% (0.8 ml/kg, oral or rectal administration, the maximum dose is 10 ml per day).

Written informed consent will be collected from each eligible participant's legal guardian prior to inclusion in the study. For eligible participants, demographic data (sex, date of birth, and laterality), family history of PCG and medical history (age of onset, initial syndrome, age at diagnosis, and medical treatment) will be recorded. Pregnancy and delivery information (gestational weeks, delivery mode, maternal drug intake and infection during pregnancy) will also be ascertained and recorded.

Randomisation

A random number table was generated by a biostatistician who will not participate in data management with the SAS V 9.3 software package (SAS Institute, Cary, NC, USA). The allocation of patients will be concealed using sequentially numbered, opaque sealed envelopes. A total of 248 envelopes will be prepared by two researchers not involved in the study. For each recruited patient, his/ her group assignment will be revealed in the operating room on the day of surgery. If a patient is deemed ineligible, then the unopened envelope will be returned to the research center, and the patient will not be randomized in the study. A surgeon will be assigned for surgical management and intraoperative data collection. The 1:1 randomization procedure will be performed in blocks of eight.

Postoperative follow-up will be performed by investigators who do not participate in patient care and have been trained to follow-up patients prior to

the study. Both surgeon(s) and investigator(s) do not communicate with each other while collecting data.

Interventions

All surgeries will be performed under general anesthesia.

Trabeculotomy

This technique has been previously described.[8] In brief, a superior quadrant fornix-based flap will be created. A 3-mm × 3-mm superficial (12 o'clock) scleral flap of three-quarters thickness will be made. A 2-mm radial incision will be made starting from the gray zone up to the white zone, followed by entering Schlemm's canal externally. An incision will be slowly deepened until the outer wall of Schlemm's canal is opened, and seeping aqueous humor is observed. Schlemm's canal will be dissected by 120° using a trabeculotome probe in both directions. The scleral flap will then be replaced with three interrupted 10-0 nylon sutures. The conjunctival flap will also be replaced with 8-0 absorbable sutures.

CTT

In the superior quadrant, CTT with MMC will be performed. A fornix-based conjunctival flap will be dissected. MMC will be applied at a concentration of 0.3mg/ ml and sustained for 3 min. Then, the area where MMC is applied will be irrigated thoroughly with balanced salt solution. A superficial scleral flap measuring 4 × 3 mm will be raised at 12 o'clock. Then, trabeculotomy will be

performed as described above. Trabeculectomy will be performed by cutting a 1-mm × 2-mm deep scleral flap, followed by a peripheral iridectomy. The scleral flap and conjunctiva will then be replaced. Finally, the anterior chamber will be reformed with balanced salt solution.

Intraoperative data, including the duration of surgery, the doses and duration of MMC used during the operation, anesthesia accidents, intraoperative complications, such as hyphema, and iris/vitreous damage, and trabeculotomy-related problems, such as failure to identify Schlemm's canal or an inability to dissect Schlemm's canal by 120 degrees, will be collected.

Postoperative treatment and patient follow-up

Patients will be treated with prednisolone acetate 1% (dexamethasone, Allergan, Parsippany-Troy Hills, NJ, USA) 6 times daily in combination with topical antibiotics (tobramycin 0.3%, s.a. ALCON-COUVREUR n.v) and pilocarpine 1% (Bausch & Lomb, Rochester, NY) 4 times daily within the first 4 weeks after the surgery.

Postoperative follow-up visits will be performed in the pediatric glaucoma clinic at Week 1, Week 2, Week 4, Month 3 and then every 3 months (±1 weeks) for 3 years. The scheduled examinations of the follow-up visits are summarized in Table 1. When necessary, chloral hydrate 10% will be applied to patients for examinations.

Table 1 Scheduled examinations of follow-up visits.

Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Examination	Base Line ± 7 d	Procedure	1 w ± 2 d	2 w ± 2 d	1 m ± 7 d	3 m ± 7 d	6 m ± 7 d	9 m ± 7 d	12 m ± 7 d	15 m ± 7 d	18 m ± 7 d	21 m ± 7 d	24 m ± 7 d	27 m ± 7 d	30 m ± 7 d	33 m ± 7 d	36 m ± 7 d
Informed content	×																
Demographics data	×																
Medical history	×																
Physical examination	×																
IOP	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
AL	×					×	×		×		×		×		×		×
HCD	×	×				×	×	×	×	×	×	×	×	×	×	×	×
Slit lamp examination	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Fundus photography	×					×	×		×		×		×		×		×
B-scan ultrasound*	×					×	×		×		×		×		×		×
refraction	×					×	×		×		×		×		×		×

VA	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
Corneal transparency	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
Corneal thickness	×															×
medications	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
Advent event		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Reoperation					×	×	×	×	×	×	×	×	×	×	×	×

* In the event of nonvisibility of fundus, B-scan ultrasound will be used to measure cupping. IOP, intraocular pressure; AL, axial length; HCD, horizontal corneal diameter; VA, visual acuity.

Outcome assessment

Primary outcome

The primary outcome is the success rate at 3 years after surgery. Complete success is defined as a postoperative IOP measure of ≥ 5 and ≤ 21 mmHg without the need for antiglaucoma medications. Qualified success is defined as the same IOP criteria with the use of glaucoma medications. Treatment failure is defined as the presence of any of the following:

1. IOP >21 mmHg with maximum medications or IOP < 5 mmHg on two consecutive follow-up visits.

   Maximal medication indicates that the patient was treated with three types of glaucoma medication or with fewer than three types of medication but could not tolerate more.

2. The occurrence of severe postoperative complications threatening vision, such as suprachoroidal hemorrhage, retinal detachment or endophthalmitis.

3. A need for reoperation to control the IOP.

Secondary outcomes

The secondary outcomes are changes in the biological parameters of eyeball (including HCD, corneal clarity, corneal thickness, C/D ratio, AL), VA, and refraction. Postoperative complications, including hyphema, shallow anterior chamber, hypotony, surgery-related iridodialysis, complicated cataract, retinal

or choroidal detachment, bleb complications (leakage or infection) and endophthalmitis, will be evaluated and recorded.

Safety consideration

The safety evaluations of the study will include complications associated with surgeries and drugs as well as adverse events. The procedures and drugs used in the study are routinely administered in daily practice. Thus, the trial has risks not exceeding usual clinical care that the patients would otherwise receive. Throughout the study, all adverse events will be recorded and managed.

Drug-related complications include unanticipated events caused by cycloplegia, anti-glaucoma drugs, and chloral hydrate. Dilation will be established following a slit lamp examination. Doctors will closely monitor the patients' pupil reflexes and vital signs after administering the medications.

Vision-threatening complications, such as suprachoroidal hemorrhage, retinal detachment, and endophthalmitis, will constitute major adverse events.

Data management and monitoring

All data collected at the scheduled follow-up visits (Table 1), will be recorded in the case report forms and entered into a digital database by trained researchers. Softcopies of digital data in the devices will be stored in a server at the end of each visit day. The completed case report forms and hardcopy data forms will be kept in locked cabinets in the research center to protect the

privacy of the participants. The implementation of the trial will be monitored by the principal investigator. Access to the final dataset will be limited to the trial administrator and the statistician.

Statistical analysis

An intention-to-treat analysis will be performed. All statistical analyses will be performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The continuous data will be expressed as the mean (SD) and analysed using the Mann-Whitney U test or independent *t* test. The categorical data will be expressed as the number of patients (percentage) or median (IQR (IQR)) and analysed using chi-square tests or Fisher's exact test.

The Kaplan-Meier method will be used to estimate a curve of the probability that the IOP is under control versus the time after surgery. The log-rank test will be employed to compare curves for the trabeculotomy and CTT groups. Comparison of continuous variables such as the HCD, AL, corneal thickness, C/D ratio, and the distribution of refractive errors between the two groups will be performed using Student's t-test or the Wilcoxon nonparametric test as appropriate, while within-group comparisons will be performed using paired t-test or Wilcoxon's signed rank test. The Chi-square test or Fisher's exact test will be used to compare the proportions of the visual outcome, the number of anti-glaucoma drugs, and complications between the two surgical groups. In addition, reasons for loss to follow-up will also be

documented.

Participant timeline

Recruitment began in the first quarter of 2015. Currently, 75% of the sample size has been attained. it is anticipated that the study will reach the recruitment target of 248 participants by the fourth quarter of 2019. The interim analysis will be conducted to evaluate one, two, and three years outcomes of trabeculotomy versus CTT for PCG.

ETHICS AND DISSEMINATION

This study was approved by ethics committee of Zhongshan Ophthalmic Center (reference number 2014MEKY023). The study protocol was also reviewed by the “5010 Plan” evaluation committee at Sun Yat-sen University, Guangzhou, China. Every year the evaluation committee will examine the study progress and adherence to the study protocol. The project leader will ensure that this study is conducted in accordance with the principles of the World Medical Association Declaration of Helsinki.

The study results will be presented at national and international meetings on ophthalmology.

DISCUSSION

This trial is a prospective, randomized, controlled intervention trial intended to provide evidence for ophthalmologists to make better decisions regarding

surgical options for patients with PCG. To the best of our knowledge, this trial is the largest clinical trial in the field of pediatric glaucoma. The findings are expected to provide evidence for whether trabeculotomy is not inferior to CTT in treating PCG with an HCD of 12-14 mm.

This trial enrolled subjects with PCG with an HCD of 12-14 mm to reduce selection bias. For PCG with an HCD less than 12 mm, the anatomic abnormality of Schlemm's canal is usually not significant, facilitating its identification during the operation. As a result, angle surgery alone is sufficient to lower IOP in these patients. Advanced PCG with an HCD greater than 14 mm is usually associated with a significant anatomic anomaly of the anterior drainage angle. The abnormally stretched anatomy of the limbus in these patients frequently makes it difficult to clearly identify the lumen of Schlemm's canal that has to be cannulated for the trabeculotomy. Thus, the success rate of trabeculotomy in advanced PCG cases is lower. Quigley *et al*[25] reported the results of trabeculotomy in 28 eyes with congenital glaucoma. The success rate in eyes with a corneal diameter greater than 14 mm was 67% compared with 100% in eyes with a smaller corneal diameter. Both conditions described above will lead to biases to the results. Moreover, most PCG cases in China are diagnosed with an HCD ranging from 12 mm to 14 mm.[7,26] These patients have a good chance to preserve useful VA if treated correctly.

No unified guideline is currently available to determine PCG severity based on corneal diameter. Kiskis *et al*[27] studied the HCD and AL in PCG

patients and concluded that HCD measurement was a more reliable guide than AL in the assessment of PCG. Currently, we are unaware of any studies comparing long-term outcomes between CTT and trabeculotomy in PCG patients with homogeneity in terms of disease severity. After considering the above information, we selected an HCD of 12-14 mm as an inclusion criterion. However, selection of surgical methods of the treatment of PCG and the evaluation of PCG severity based only on HCD are issues requiring further investigations and improvement.

In conclusion, this trial is a large clinical trial aiming to provide evidence for the optimum first-line surgery for patients with PCG with an HCD of 12-14 mm. If the trabeculotomy group is associated with comparable surgical success and fewer postoperative complications compared with CTT group, trabeculotomy should be recommended as a primary surgical treatment for PCG with an HCD of 12-14 mm, saving trabeculectomy for future intervention. In addition, complications associated with trabeculectomy will be reduced. The visual outcome in this trial may help provide insight into the effects of surgical methods on VA. The findings of our study are expected to provide guidance to clinicians weighing the benefit and risk of trabeculotomy compared to CTT for the treatment of PCG.

Acknowledgments

We would like to thank all research assistants and nursing staff involved in this

trial, who contributed to the practical organization and execution of this study.

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Author Contributions XL conceived the study and is the project leader for the trial. XL, XXG, YFY, JJH, YMZ, XXC and LF participated in the study design and recruited the patients. LF wrote the manuscript. XL, XXG, and XYX critically revised the manuscript. JZ designed the database system and performed the statistics-related design. All authors read and approved the final manuscript.

Funding statement This study was supported by the Sun Yat-Sen University Clinical Research 5010 Program (2014016) and the National Natural Science Foundation of China (81800879). The sponsor had no role in the protocol design or conduct of this study.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was approved by ethics committee of Zhongshan Ophthalmic Center (reference number 2014MEKY023). The study protocol was also reviewed by the "5010 Plan" evaluation committee at Sun Yat-sen University, Guangzhou, China.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

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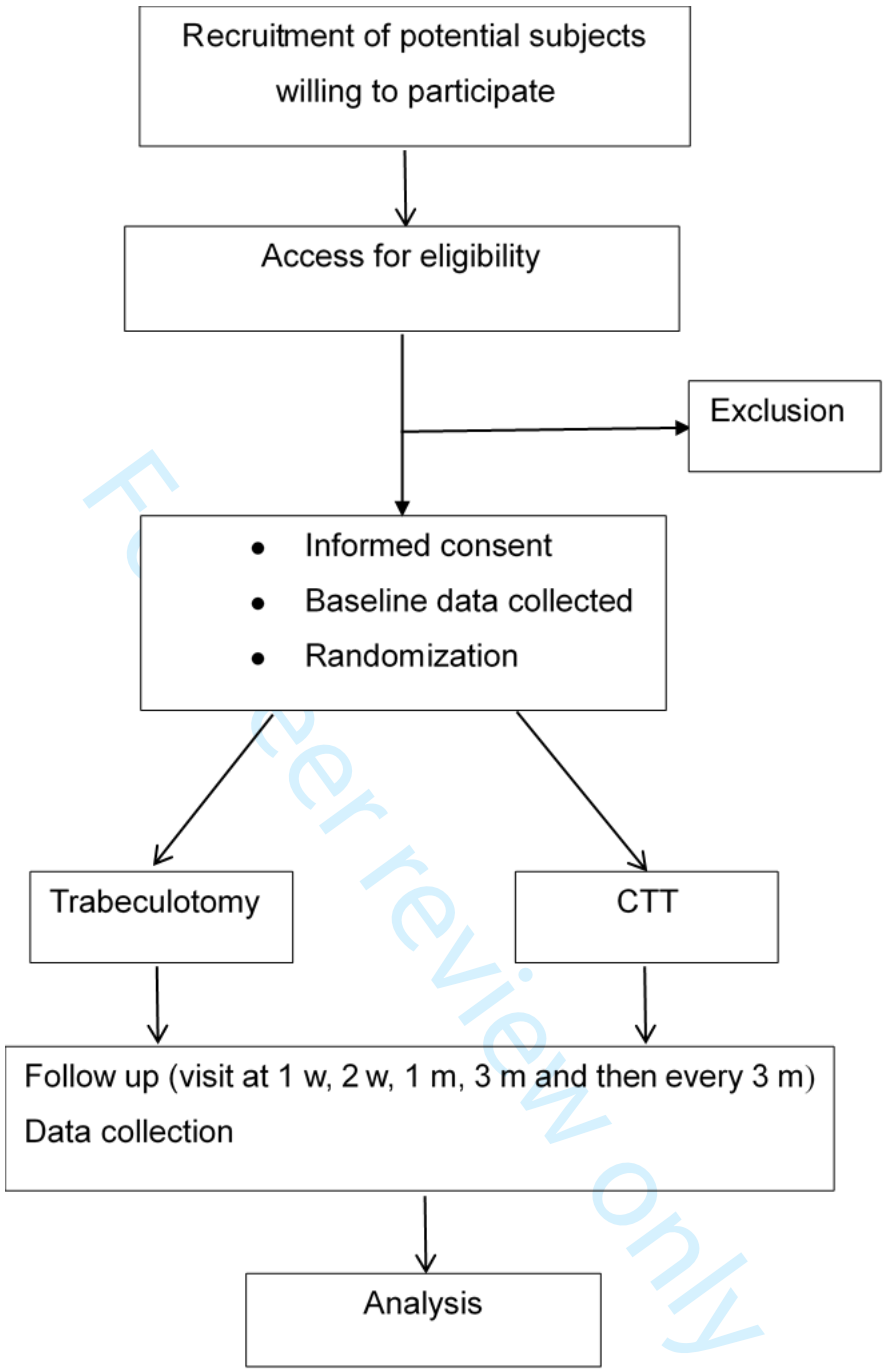
Figure Legend

Figure 1 Flowchart of the study. CTT, combined trabeculotomy-trabeculectomy.



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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,23
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	23
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6.7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	7,8

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13,14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	17,18
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	20, Table1

		(see Figure)	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12,13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-11, Table1
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	18,19

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	20
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	18

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18,19
Declaration of	#28	Financial and other competing interests for principal	23

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for Primary Congenital Glaucoma: Study Protocol of a Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032957.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Dec-2019
Complete List of Authors:	Fang, Lei; Sun Yat-Sen University Zhongshan Ophthalmic Center Guo, Xinxing; Sun Yat-Sen University Zhongshan Ophthalmic Center; Johns Hopkins Wilmer Eye Institute Yang, Yangfan; Sun Yat-Sen University Zhongshan Ophthalmic Center Zhang, Jian; Sun Yat-Sen University Zhongshan Ophthalmic Center Chen, Xiangxi; Sun Yat-Sen University Zhongshan Ophthalmic Center; Wuhan Aier Eye Hospital Zhu, Yingting; Sun Yat-Sen University Zhongshan Ophthalmic Center, Department of Glaucoma Huang, Jielei; Sun Yat-Sen University Zhongshan Ophthalmic Center; Zhongshan Aier Eye Hospital Huang, Jingjing; Sun Yat-Sen University Zhongshan Ophthalmic Center Zhong, Yimin; Sun Yat-Sen University Zhongshan Ophthalmic Center Xu, Xiaoyu; Sun Yat-Sen University Zhongshan Ophthalmic Center Liu, Xing; Sun Yat-Sen University Zhongshan Ophthalmic Center, Glaucoma
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Ophthalmology, Paediatrics, Surgery
Keywords:	Primary congenital glaucoma, Trabeculotomy, PCG, Combined trabeculotomy-trabeculectomy, Randomized controlled trial

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Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for Primary Congenital Glaucoma: Study Protocol of a Randomized Controlled Trial

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Word count: 3820

Abstract

Introduction: Trabeculotomy and combined trabeculotomy-trabeculectomy (CTT) are major surgical options for primary congenital glaucoma (PCG). However, it is unclear which of these two surgical procedures should be recommended as the optimum first-line treatment for PCG. This trial aims to determine whether the surgical outcomes of trabeculotomy are noninferior to those of CTT in PCG with a horizontal corneal diameter (HCD) of 12-14 mm.

Methods and analysis: This is a 3-year, noninferiority, prospective, randomized controlled trial. We plan to recruite 248 participants (aged ≤ 3 years) with PCG with an HCD of 12-14 mm from the Department of Glaucoma, Zhongshan Ophthalmic Center, Guangzhou, China. One eye per participant will be randomly (1:1) assigned to receive trabeculotomy or CTT. The primary outcome is the 3-year postoperative success rate in lowering IOP, and the secondary clinical outcomes will include IOP reduction, visual acuity (VA), HCD, central corneal thickness, axial length, cup-disc ratio, refractive error, and postoperative complications. Data will be analyzed by the intention-to-treat principle.

Ethical approval and dissemination: The study protocol has been approved by the ethics committee of Zhongshan Ophthalmic Center (2014MEKY023) and the “5010 Plan” evaluation committee at Sun Yat-Sen University, Guangzhou, China. The results will be disseminated in international academic

meetings and published in peer-reviewed journals.

Trial registration: Chinese Clinical Trial Registry, ChiCTR-IOR-14005588; Date registered: 20 November 2014.

Keywords: PCG, Primary congenital glaucoma, Trabeculotomy, Combined trabeculotomy-trabeculectomy, Randomized controlled trial

Article Summary

Strengths and limitations of this study

- The trial design is prospective, randomized and controlled with a relatively large sample size, and the follow-up is comparatively long (3 years).
- The study is the first randomized controlled trial to comprehensively evaluate the surgical and visual outcomes of trabeculotomy and CTT in PCG patients with an HCD of 12 to14 mm.
- This study assesses important clinical measurements with significant clinical implications, including HCD, axial length, central corneal thickness, C/D ratio, refractive errors and VA. All data will be obtained following standardized protocols and assessed longitudinally.
- The IOP criteria ($\leqslant$ 21 mmHg) used to define glaucoma and surgical success rate may be relatively high for children younger than 3 years old.
- Instead of the gold applanation tonometry, IOP is measured by Tono-Pen tonometry.

INTRODUCTION

Primary congenital glaucoma (PCG) is one of main causes of blindness in children. Liu *et al*[1] reported that congenital glaucoma accounted for 5.1% of all congenital ocular diseases in a Chinese population. It is estimated to account for 0.01–0.04% of blindness worldwide.[2] In India, this disease accounts for 4.2% of all childhood blindness.[2] Haddad *et al*[3] evaluated 3210 visually impaired children and found that PCG was responsible for 10.2% of visual impairments. Since at least 50% of eyes with PCG presenting at birth will become legally blind, patients with PCG require prompt treatment and follow-up examinations throughout their lives.[4]

Surgical intervention is the main treatment for PCG. Goniotomy and trabeculotomy are considered initial procedures because of their high success rates.[5,6] However, Clear corneal is a premise for goniotomy but not necessarily for trabeculotomy. Trabeculotomy reduces intraocular pressure (IOP) by tearing the trabecular meshwork into the anterior chamber. Regarding complications, hyphema is more common in trabeculotomy but can resolve spontaneously and cause no additional problems.[7-9]

Combined trabeculotomy-trabeculectomy (CTT) has been advocated for treating moderate to severe congenital glaucoma.[10] The rationale for CTT is to gain access to the dual outflow through Schlemm's canal and the trabeculectomy fistula. The application of Mitomycin-C (MMC) can improve the

surgical success rates of CTT,[11] which is, however, disputed by some other studies.[12,13] Complications after CTT surgery, such as hyphema, bleb-related infections, and choroidal detachment, have been reported.[14]

Although some studies have indicated that trabeculotomy and CTT are equally effective in lowering IOP,[7,9,15] their results were inconsistent with others.[10,16] There is a paucity of randomized controlled trials with large sample sizes that compare the results of trabeculotomy with CTT for PCG. A randomized trial conducted by Khalil *et al*[9] included a cohort of 28 eyes of 28 children younger than 2 years old with a mean follow-up time of 3 years. They concluded that both trabeculotomy and CTT with MMC had similar outcomes. However, due to limitations of sample sizes, it remains inconclusive as which procedure is preferable.[17]

The horizontal corneal diameter (HCD) is typically increased in PCG patients, which serves as an indication for disease severity and a key factor for surgery selection.[18] In general, angle surgeries are recommended for PCG with an HCD <12 mm.[8] Trabeculectomy or CTT with or without the use of MMC is usually chosen for advanced cases with an HCD exceeding 14 mm.[7,19] For PCG with an HCD of 12-14 mm, trabeculotomy and CTT are the two major surgical options. However, it remains unknown whether trabeculotomy, when compared to CTT, yields comparable results and fewer postoperative complications in PCG with an HCD of 12-14 mm. Therefore, we design a study to determine whether the clinical outcomes of trabeculotomy are noninferior to

those of CTT for PCG with an HCD of 12-14 mm.

Study objectives

The primary outcome of our study is to compare the 3-year success rate in lowering IOP between trabeculotomy and CTT in patients with PCG with an HCD of 12-14 mm. The secondary outcome is to assess changes in IOP and the morphometric parameters of the eyeball, visual outcomes and postoperative complications in these two surgical procedures.

METHODS AND ANALYSIS

This protocol is developed in line with the Standard Protocol Items Recommendations for Interventional Trails (SPIRIT). The SPIRIT checklist for the protocol is available as 'supplement'. The trail was registered at the Chinese Clinical Trail Registry (www.Chictr.org.cn) on 20, November 2014 with a trial identification of ChiCTR-IOR-14005588. Protocol of this trial was approved on 25 August 2014.

Trial design and setting

This study is a 3-year, prospective, randomized, single-center, noninferiority trial comparing clinical outcomes and postoperative complications between trabeculotomy and CTT in treating PCG with an HCD of 12- 14 mm. Eligible patients will be enrolled and randomly assigned to receive either trabeculotomy or CTT (figure 1). The trial is being conducted at the Zhongshan Ophthalmic Center, Guangzhou, China.

Participant selection

Inclusion criteria

Participants will be included if they meet all of the following criteria: (1) diagnosis of PCG in either eye, (2) equal to or under 3 years of age, (3) HCD between 12 and 14 mm, and (4) no previous intraocular surgery or laser treatment.

PCG is defined as follows:[20]

1. Age ≤ 3 years old.
2. IOP >21 mmHg.
3. Absence of other ocular or systemic diseases.
4. Combined with one or more of the following clinical signs: (1) corneal findings: Haab's striae, corneal edema, corneal diameters >11 mm in the newborns, >12mm in children younger than 1 year old, and >13mm in children older than 1 year old; (2) increased (>0.3) or asymmetric (>0.2) C/D ratio; and (3) abnormally increased axial length (AL).

Normal AL is as follows: 3 mo-3yrs: 19-22 mm.[21]

Only one eye per patient will be enrolled. If both eyes of a patient are eligible for the study, the eye with the higher baseline IOP will be selected. The treatment for the fellow eye will be determined at the physician's discretion.

Exclusion criteria

Patients will be excluded if they meet any of the following criteria:

- Inability of the patients' legal guardian to give informed consent.
- Inability of the patient to return to the clinic for the scheduled study visits.
- Contraindications to anesthesia or surgery for ocular disease.
- Severe corneal cloudiness precluding anterior chamber visualization.
- Secondary congenital glaucoma.
- Other coexisting ocular diseases such as an abnormal cornea, congenital iris abnormality, congenital cataract, or retinopathy of prematurity.

Withdrawal criteria

1. Failure to locate or dissect Schlemm's canal by 120°.
2. The presence of any of the following issues during the operation: severe anesthesia accident, suprachoroidal hemorrhage, or a change in the operative procedure according to the patient's condition.
3. A desire to quit the trial.

The withdrawal criteria described above have been established to ensure that the outcomes of the two procedures (trabeculotomy and CTT) will be effectively analyzed for the full 3-year duration of the study.

Interventions

All surgeries will be performed under general anesthesia by attending

surgeons.

Trabeculotomy

This technique has been previously described.[8] In brief, a superior quadrant fornix-based flap will be created. A 3-mm × 3-mm superficial (12 o'clock) scleral flap of three-quarters thickness will be made. A 2-mm radial incision will be made starting from the gray zone up to the white zone, followed by entering Schlemm's canal externally. An incision will be slowly deepened until the outer wall of Schlemm's canal is opened and seeping aqueous humor is observed. Schlemm's canal will be dissected by 120° in both directions using a trabeculotome probe. The scleral flap will then be replaced with three interrupted 10-0 nylon sutures. The conjunctival flap will also be replaced with 8-0 absorbable sutures.

CTT

In the superior quadrant, CTT with MMC will be performed. A fornix-based conjunctival flap will be dissected. After dissection of a superficial (12 o'clock) scleral flap measuring 4 × 3 mm^2, MMC (0.3 mg/ ml) soaked pieces of microsponge will be applied under the scleral flap and the conjunctiva for 3 min, and the area will then be washed thoroughly with balanced salt solution. Then, trabeculotomy will be performed as described above. Trabeculectomy will be performed by cutting a 1-mm × 2-mm deep scleral flap, followed by a peripheral iridectomy. The scleral flap and conjunctiva will then be replaced.

Finally, the anterior chamber will be reformed with balanced salt solution.

Intraoperative data, including the duration of surgery, the doses and duration of MMC used during the operation, anesthesia accidents, intraoperative complications, such as hyphema, iris/vitreous damage, and trabeculotomy-related problems, such as failure to identify Schlemm's canal or an inability to dissect Schlemm's canal by 120 degrees, will be collected.

Postoperative treatment and patient follow-up

Patients will be treated with prednisolone acetate 1% (Allergan, Parsippany-Troy Hills, NJ, USA) 6 times daily in combination with topical antibiotics (tobramycin 0.3%, s.a. ALCON-COUVREUR n.v) and pilocarpine 1% (Bausch & Lomb, Rochester, NY) 4 times daily for the first 4 weeks after the surgery.

Postoperative follow-up visits will be performed in the pediatric glaucoma clinic at Week 1, Week 2, Week 4, Month 3 and then every 3 months (±1 weeks) for 3 years. The scheduled examinations of the follow-up visits are summarized in Table 1. Chloral hydrate 10% (0.8 ml/kg, oral or rectal administration, the maximum dose is 10 ml per day) will be applied to patients not compliant for examinations.

If IOP is found to be high at a scheduled visit, topical antiglaucoma medication will be prescribed and the scheduled follow-up interval (if longer than 2 weeks) will be shortened to 2 weeks. Additional surgery will be performed if the IOP is

> 21 mmHg on maximum anti-glaucoma medications (including pilocarpine 1%, brinzolamide 1%, and latanoprost 0.005%) in two consecutive study visits.

Table 1 Scheduled examinations of follow-up visits.

Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Examination	Baseline	Procedure	1 w ± 2 d	2 w ± 2 d	1 m ± 7 d	3 m ± 7 d	6 m ± 7 d	9 m ± 7 d	12 m ± 7 d	15 m ± 7 d	18 m ± 7 d	21 m ± 7 d	24 m ± 7 d	27 m ± 7 d	30 m ± 7 d	33 m ± 7 d	36 m ± 7 d
Informed consent	×																
Demographic data	×																
Medical history	×																
Physical examination	×																
IOP	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
AL	×					×	×		×		×		×		×		×
HCD	×	×			×	×	×	×	×	×	×	×	×	×	×	×	×
Slit lamp examination	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Fundus photography	×					×	×		×		×		×		×		×
B-scan ultrasound*	×					×	×		×		×		×		×		×
Refraction	×					×	×		×		×		×		×		×

VA	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
Corneal transparency	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
CCT	×															×
Medications	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
Adverse events		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Reoperation					×	×	×	×	×	×	×	×	×	×	×	×

* In the event of nonvisibility of the fundus, B-scan ultrasound will be used to measure cupping. IOP, intraocular pressure; AL, axial length; HCD, horizontal corneal diameter; VA, visual acuity; CCT, central corneal thickness.

Outcome assessment

Primary outcome

The primary outcome is the success rate in lowering IOP at 3 years after surgery. Success is defined as:

1. IOP≥ 5 mmHg and ≤ 21 mmHg on two consecutive follow-up visits with or without anti-glaucoma medications.[5, 22]

2. The absence of severe vision-threatening postoperative complications, such as suprachoroidal hemorrhage, retinal detachment or endophthalmitis.

3. No need for additional surgical intervention to control the IOP.

Complete success is defined as meeting success criteria without the need for anti-glaucoma medications. Qualified success is defined as meeting success criteria with the use of anti-glaucoma medications.

Secondary outcomes

The secondary outcomes will be evaluated by IOP reduction and changes in the morphometric and functional parameters of eyeball: HCD, corneal transparency, CCT, C/D ratio, AL, VA, and refraction. Postoperative complications, including hyphema, shallow anterior chamber, hypotony, surgery-related iridodialysis, complicated cataract, retinal or choroidal detachment, bleb complications (leakage or infection) and endophthalmitis, will be evaluated and recorded.

Sample size calculation

The sample calculation was based on the hypothesis that the 3-year success rate of trabeculotomy will be noninferior to that of CTT. Published studies have shown that the success rate at the 3rd year after CTT ranges from 72.6% to 87%.[1,9,23,24] We assume that the 3-year success rate of CTT will be approximately 80%. Therefore, 224 subjects (112 per group) will be needed to provide the trial with a power of at least 80% to demonstrate the noninferiority (-15% margin) of trabeculotomy to CTT (one-sided α value: 0.025). Assuming a 10% loss to follow-up, a sample size of 248 participants is required for this study, with 124 participants in each group.

Patient recruitment and baseline data collection

All subjects will first be assessed for potential participation in the study by the primary investigator. Patients who gave consent to the study will be invited to undergo enrollment examinations to determine enrollment status.

Examinations

IOP. IOP will be measured with a Tono-Pen Avia (Reichart, Depew, New York, USA) under sedation with chloral hydrate 10% and topical anesthesia. Although the use of anesthetic agents during examination under anesthesia (EUA) may influence IOP and affect the accuracy of IOP documentation, chloral hydrate has been shown to have a minimal effect on IOP in pediatric ophthalmic examinations.[18]

Slit-lamp examination. The condition of the anterior segment, including corneal clarity, corneal edema, Haab's striae, anterior chamber depth, iris, pupil, and lens, will be evaluated using a hand-held slit lamp (Keeler, Bucks, England).

Corneal clarity will be recorded as mild (iris texture clearly seen), moderate (iris seen but texture not clearly visible), and severe (iris not visible).

HCD. A caliper will be used to measure the HCD (white to white) by ophthalmologists. Participants with an HCD less than 12 mm or greater than 14 mm will be excluded.

Central corneal thickness (CCT). CCT will be measured using ultrasound pachymetry (IOPac, Heidelberg Engineering, Heidelberg, Germany). Topical anesthetic will be used prior to the application of the ultrasonic probe to the corneal surface. All measurements were taken with the child in the supine position. Ten measurements will be taken for each eye, and the lowest reading will be recorded.

C/D ratio. The C/D ratio will be evaluated using direct ophthalmoscopy (66 Vision, Suzhou, China) as permitted by the media clarity. Images showing the C/D ratio will be obtained using a hand-held retinal camera (Kowanonmyd a-D III; KowaOptimedInc, Aichi, Japan) through a dilated pupil. For children with hazy media, whose fundus cannot be visualized, a B-scan ultrasound (Quantel Medical, CF, France) will be used to rule out any intraocular pathology and to detect excavation of the optic nerve head.

Ocular biometry. Ocular biometry, including AL, anterior chamber depth, lens thickness, and vitreous chamber depth, will be measured using A-scan ultrasound (Quantel Medical, CF, France). Ten repeated measurements will be taken and averaged for analysis.

Visual acuity (VA). VA will be measured using suitable procedures. Teller acuity cards (Vistech Consultants, Inc. Dayton, OH, USA) will be utilized at a distance of 55 cm in nonverbal children. The Lea symbols (Precision Vision, La Salle, IL) with a test distance of 3 meters and the Early Treatment of Diabetic Retinopathy Study (ETDRS) LogMAR E chart (Precision Vision, Villa Park, Illinois, USA) with a test distance of 4 meters will be employed for verbal children. Monocular VA will be assessed in the right eye followed by the left eye. For children who cannot complete the quantified VA examinations mentioned above, the ability to fix and follow light will be evaluated.

Refractive error. Refraction will be measured by retinoscopy after cycloplegia. Cycloplegia will be induced with two drops of cyclopentolate 1% instilled 5 min apart, with a third drop administered after 20 min. Cycloplegia will be then evaluated after an additional 15 min. Cycloplegia is considered complete if the pupil dilates to ≥ 6 mm and a light reflex is absent.[25]

All ophthalmological examinations described above will be performed in both eyes. Chloral hydrate 10% will be applied to patients not compliant for examinations.

Written informed consent will be collected from each eligible participant's legal guardian prior to inclusion in the study. For eligible participants, demographic data (sex, date of birth, and laterality), family history of PCG and medical history (age of onset, initial syndrome, age at diagnosis, and medical treatment) will be recorded. Pregnancy and delivery information (gestational weeks, delivery mode, maternal drug intake and infection during pregnancy) will also be ascertained and recorded.

Randomization

A randomization list was generated with the SAS V 9.3 software package (SAS Institute, Cary, NC, USA) by a biostatistician who will not participate in data management. The 1:1 randomization procedure will be performed using varying block sizes. To ensure concealment, the block size will not be disclosed. The allocation of patients will be concealed using sequentially numbered, opaque sealed envelopes. A total of 248 envelopes will be prepared by two researchers not involved in the study. For each recruited patient, his/her group assignment will be revealed in the operating room on the day of surgery. Surgical management and intraoperative data will be collected.

Postoperative follow-up will be performed by investigators who will not participate in patient care and are trained to follow-up patients prior to the study. The surgeon(s) and investigator(s) will not communicate with each other while collecting data.

Data management and monitoring

All data collected at the scheduled follow-up visits (Table 1) will be recorded in the case report forms and entered into a digital database by trained researchers. The soft copies of digital data will be stored in these devices and then in a server at the end of each visit day. The completed case report forms and hardcopy data forms will be kept in locked cabinets in the research center. The implementation of the trial will be monitored by the principal investigator. Access to the final dataset will be limited to the trial administrator and the statistician.

Statistical analysis

All statistical analyses will be performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables conformed to the normal distribution will be expressed as the mean (SD). Dichotomous and nominal variables will be expressed as frequencies, ordinal and discrete variables as median and IQR.

The primary analysis will be based on the principle of intention-to-treat (ITT) and will include all subjects who underwent randomization, with data censored at the last schedule visit. We will perform a sensitivity analysis of the post hoc worst-case scenario, in which subjects who did not complete follow-up were considered failed outcomes, and a sensitivity analysis of a post hoc complete-case scenario, in which only subjects who had complete data all

through the trail will be included. We calculated 95% confidence interval for the estimates of the absolute differences between the two treatment groups regarding the 3-year success rate using the Cochran-Mantel-Haenszel method. Noninferiority would be met if the lower limit of the 95% CI of the absolute difference did not cross the prespecified noninferiority margin (-15%). The survival data (time-to-IOP controlled) will be analyzed using the Kaplan-Meier method. The log-rank test will be employed to compare curves in the trabeculotomy and CTT groups.

Secondary outcomes will be assessed with two-sided tests. Comparisons of continuous variables distributed normally, such as the IOP, HCD, AL, and CCT will be performed between the two groups using Student's t-test. For continuous variables not distributed normally and for discrete variables (including the C/D ratio, number of anti-glaucoma drugs, and distribution of refractive errors) between the two groups comparison will be performed using Mann-Whitney U test. The Chi-square test or Fisher's exact test will be used to compare the proportions of the visual outcomes, and complications between the two surgical groups.

Safety consideration

The safety evaluations of the study will include complications associated with surgeries as well as drugs adverse events. The procedures and drugs used in the study are routinely administered in daily practice. Thus, the trial has risks

not exceeding usual clinical care that the patients would otherwise receive. Throughout the study, all adverse events will be recorded and managed.

Drug-related complications include unanticipated events caused by cycloplegia, anti-glaucoma drugs, and chloral hydrate. Dilation will be established following a slit lamp examination. Doctors will closely monitor the patients' pupil reflexes and vital signs after administering the medications.

Vision-threatening complications, such as suprachoroidal hemorrhage, retinal detachment, and endophthalmitis, will constitute major adverse events.

Trial status

Recruitment began in the first quarter of 2015. Currently, 75% of the sample size has been attained. it is anticipated that the study will reach the recruitment target of 248 participants by the fourth quarter of 2019. There are no plans for interim analysis.

PATIENT AND PUBLIC INVOLVEMENT

Patients and public were not involved in the design of the study.

ETHICS AND DISSEMINATION

This study was approved by the ethics committee of Zhongshan Ophthalmic Center (reference number 2014MEKY023). The study protocol was also reviewed by the "5010 Plan" evaluation committee at Sun Yat-sen University, Guangzhou, China. Every year, the evaluation committee will examine the

study progress and its adherence to the study protocol. Any important modifications to the protocol will be documented in the study protocol as formal amendments. Such amendments will be submitted to the ethics committee of Zhongshan Ophthalmic Center and the “5010 Plan” evaluation committee of the Sun Yat-sen University for a review. The project leader will ensure that this study is conducted in accordance with the principles of the World Medical Association Declaration of Helsinki.

The study results will be presented at national and international meetings on ophthalmology.

DISCUSSION

This is a prospective, randomized, controlled intervention trial aims to provide evidence for clinicians for to better judgement regarding surgical options for patients with PCG. To the best of our knowledge, this trial is the largest clinical trial in the field of pediatric glaucoma. The findings are expected to provide evidence indicating whether trabeculotomy is noninferior to CTT in treating PCG with an HCD of 12-14 mm.

For PCG with an HCD less than 12 mm, the anatomic abnormality of Schlemm’s canal is usually not significant, facilitating its identification during the operation. As a result, angle surgery alone is sufficient to lower IOP in these patients. Sampaolesi et al[26] proposed that trabeculotomy is suitable for children with PCG in whom the corneal diameter is less than13 mm and the AL

is less than 23 mm. Advanced PCG with an HCD greater than 14 mm is usually associated with a significant anatomic anomaly of the anterior drainage angle. The abnormally stretched anatomy of the limbus in these patients frequently makes it difficult to clearly identify the lumen of Schlemm's canal that has to be cannulated for the trabeculotomy. Thus, the success rate of trabeculotomy is lower in advanced PCG cases. Quigley *et al*[27] reported the results of trabeculotomy in 28 eyes with congenital glaucoma. The success rate in eyes with an HCD greater than 14 mm was 67% compared with 100% in eyes with a smaller HCD. Both of the conditions described above will lead to biases in the results. Moreover, most PCG cases in China have an HCD ranging from 12 mm to 14 mm,[7,28] and these patients have a good chance of preserving useful VA if treated correctly.

No unified guideline is currently available to determine PCG severity based on corneal diameter. Cronemberger et al[29] confirmed that a higher HCD will trigger higher HCD and AL at final follow-up. Kiskis *et al*[30] studied the HCD and AL in PCG patients and concluded that HCD measurement was a more reliable guide than AL in the assessment of PCG. Currently, we are unaware of any studies that compared long-term outcomes between CTT and trabeculotomy in PCG patients who exhibited homogeneity in terms of disease severity. After considering the above information, we selected an HCD of 12-14 mm as an inclusion criterion. However, selection of surgical methods for the treatment of PCG and the evaluation of PCG severity based on HCD alone

are issues requiring further investigation and improvement.

With regard to IOP, we selected an IOP value of ≤ 21 mmHg as a success criterion based on the previous reports.[5, 23, 31] In this study, IOP will be measured with Tono-pen which has been widely used in clinic for many years. We chose Tono-pen as the measurement by referring to the previous studies.[32-34] On the other hand, Tono-pen is particularly useful with corneal scars or edema,[35] which are often seen in PCG eyes. We used Tono-pen for all patients at each scheduled visit, which eliminated any possibility of bias due to the use of different tonometry techniques in different patients.

In conclusion, this is a large clinical trial aiming to provide evidence for the optimum first-line surgery for patients with PCG with an HCD of 12-14 mm. If the trabeculotomy group is associated with comparable surgical success and fewer postoperative complications compared with CTT group, trabeculotomy should be recommended as a primary surgical treatment for PCG with an HCD of 12-14 mm, saving trabeculectomy for future intervention. In addition, complications associated with trabeculectomy will be reduced. The visual outcome in this trial may help provide insight into the effects of surgical methods on VA. The findings of our study are expected to provide guidance to clinicians weighing the benefit and risk of trabeculotomy compared to CTT for the treatment of PCG.

Acknowledgments

We would like to thank all of the research assistants and nursing staff involved in this trial for contributing to the practical organization and execution of this study.

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Author Contributions XL conceived the study and is the project leader for the trial. XL, XXG, YFY, JJH, YMZ, XXC, JlH and LF participated in the study design and recruited the patients. LF wrote the manuscript. XL, XXG, YTZ, and XYX critically revised the manuscript. JZ designed the database system and performed the statistics-related design. All authors read and approved the final manuscript.

Funding statement This study was supported by the Sun Yat-Sen University Clinical Research 5010 Program (2014016) and the National Natural Science Foundation of China (81800879). The sponsor had no role in the protocol design or conduct of this study.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was approved by the ethics committee of Zhongshan Ophthalmic Center (reference number 2014MEKY023). The study protocol was also reviewed by the "5010 Plan" evaluation committee at Sun Yat-sen University, Guangzhou, China.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

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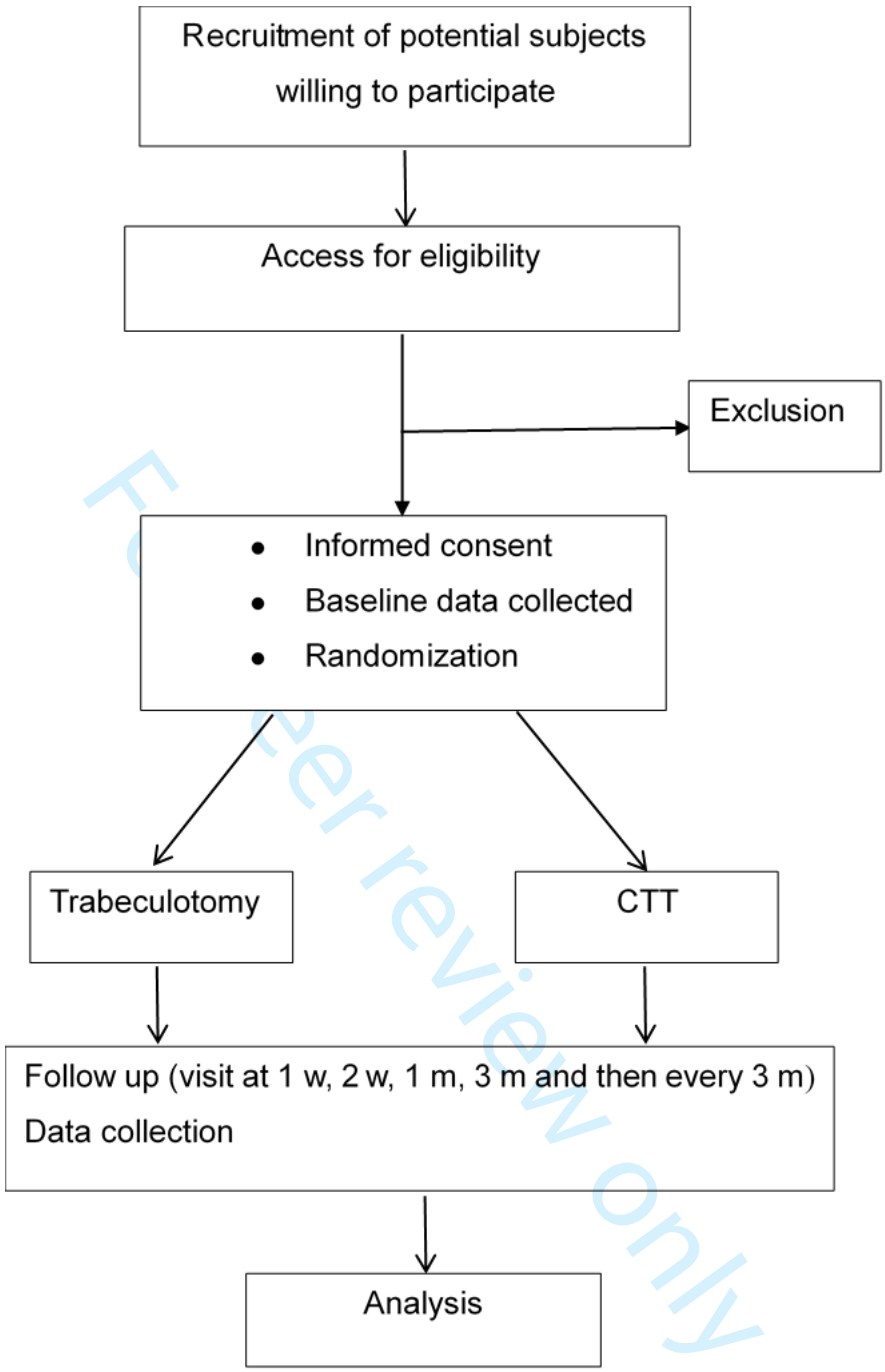
Figure Legend

Figure 1 Flowchart of the study. CTT, combined trabeculotomy-trabeculectomy.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,24-25
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1,25
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	7,8

		individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended	10, Table1

		(see Figure)	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	18
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	18
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	18

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	18
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-18, Table1
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	19

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	22

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21-22
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of	#28	Financial and other competing interests for principal	25

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	25
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for Primary Congenital Glaucoma: Study Protocol of a Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032957.R2
Article Type:	Protocol
Date Submitted by the Author:	21-Jan-2020
Complete List of Authors:	Fang, Lei; Sun Yat-Sen University Zhongshan Ophthalmic Center Guo, Xinxing; Sun Yat-Sen University Zhongshan Ophthalmic Center; Johns Hopkins Wilmer Eye Institute Yang, Yangfan; Sun Yat-Sen University Zhongshan Ophthalmic Center Zhang, Jian; Sun Yat-Sen University Zhongshan Ophthalmic Center Chen, Xiangxi; Sun Yat-Sen University Zhongshan Ophthalmic Center; Wuhan Aier Eye Hospital Zhu, Yingting; Sun Yat-Sen University Zhongshan Ophthalmic Center, Department of Glaucoma Huang, Jielei; Sun Yat-Sen University Zhongshan Ophthalmic Center; Zhongshan Aier Eye Hospital Huang, Jingjing; Sun Yat-Sen University Zhongshan Ophthalmic Center Zhong, Yimin; Sun Yat-Sen University Zhongshan Ophthalmic Center Xu, Xiaoyu; Sun Yat-Sen University Zhongshan Ophthalmic Center Liu, Xing; Sun Yat-Sen University Zhongshan Ophthalmic Center, Glaucoma
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Ophthalmology, Paediatrics, Surgery
Keywords:	Primary congenital glaucoma, Trabeculotomy, PCG, Combined trabeculotomy-trabeculectomy, Randomized controlled trial

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Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for Primary Congenital Glaucoma: Study Protocol of a Randomized Controlled Trial

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Word count: 3896

Abstract

Introduction: Trabeculotomy and combined trabeculotomy-trabeculectomy (CTT) are major surgical options for primary congenital glaucoma (PCG). However, it is unclear which of these two surgical procedures should be recommended as the optimum first-line treatment for PCG. This trial aims to determine whether the outcomes of trabeculotomy are noninferior to those of CTT in moderate PCG with a horizontal corneal diameter (HCD) of 12-14 mm.

Methods and analysis: This is a 3-year, noninferiority, prospective, randomized controlled trial. We plan to recruite 248 participants (aged ≤ 3 years) with PCG with an HCD of 12-14 mm from the Department of Glaucoma, Zhongshan Ophthalmic Center, Guangzhou, China. One eye per participant will be randomly (1:1) assigned to receive trabeculotomy or CTT. The primary outcome is the 3-year postoperative success rate in lowering IOP, and the secondary clinical outcomes will include IOP reduction, visual acuity (VA), HCD, central corneal thickness, axial length, cup-disc ratio, refractive error, and postoperative complications. Data will be analyzed by the intention-to-treat principle.

Ethical approval and dissemination: The study protocol has been approved by the ethics committee of Zhongshan Ophthalmic Center (2014MEKY023) and the “5010 Plan” evaluation committee at Sun Yat-Sen University, Guangzhou, China. The results will be disseminated in international academic meetings and

published in peer-reviewed journals.

Trial registration: Chinese Clinical Trial Registry, ChiCTR-IOR-14005588; Date registered: 20 November 2014.

Keywords: PCG, Primary congenital glaucoma, Trabeculotomy, Combined trabeculotomy-trabeculectomy, Randomized controlled trial

Article Summary

Strengths and limitations of this study

- The trial design is prospective, randomized and controlled with a relatively large sample size, and the follow-up is comparatively long (3 years).
- The study is the first randomized controlled trial to comprehensively evaluate the surgical and visual outcomes of trabeculotomy and CTT in PCG patients with an HCD of 12 to14 mm.
- This study assesses important clinical measurements with significant clinical implications, including HCD, axial length, central corneal thickness, C/D ratio, refractive errors and VA. All data will be obtained following standardized protocols and assessed longitudinally.
- The IOP criteria ($\leqslant$ 21 mmHg) used to define glaucoma and surgical success rate may be relatively high for children younger than 3 years old.
- Instead of the gold applanation tonometry, IOP is measured by Tono-Pen tonometry.

INTRODUCTION

Primary congenital glaucoma (PCG) is one of main causes of blindness in children. Liu *et al*[1] reported that congenital glaucoma accounted for 5.1% of all congenital ocular diseases in a Chinese population. It is estimated to account for 0.01–0.04% of blindness worldwide.[2] In India, this disease accounts for 4.2% of all childhood blindness.[2] Haddad *et al*[3] evaluated 3210 visually impaired children and found that PCG was responsible for 10.2% of visual impairments. Since at least 50% of eyes with PCG presenting at birth will become legally blind, patients with PCG require prompt treatment and follow-up examinations throughout their lives.[4]

Surgical intervention is the main treatment for PCG. Goniotomy and trabeculotomy are considered initial procedures because of their high success rates.[5,6] However, Clear corneal is a premise for goniotomy but not necessarily for trabeculotomy. Trabeculotomy reduces intraocular pressure (IOP) by tearing the trabecular meshwork into the anterior chamber. Regarding complications, hyphema is more common in trabeculotomy but can resolve spontaneously and cause no additional problems.[7-9]

Combined trabeculotomy-trabeculectomy (CTT) has been advocated for treating moderate to severe congenital glaucoma.[10] The rationale for CTT is to gain access to the dual outflow through Schlemm's canal and the trabeculectomy fistula. The application of Mitomycin-C (MMC) can improve the

surgical success rates of CTT,[11] which is, however, disputed by some other studies.[12,13] Complications after CTT surgery, such as hyphema, bleb-related infections, and choroidal detachment, have been reported.[14]

Although some studies have indicated that trabeculotomy and CTT are equally effective in lowering IOP,[7,9,15] their results were inconsistent with others.[10,16] There is a paucity of randomized controlled trials with large sample sizes that compare the results of trabeculotomy with CTT for PCG. A randomized trial conducted by Khalil *et al*[9] included a cohort of 28 eyes of 28 children younger than 2 years old with a mean follow-up time of 3 years. They concluded that both trabeculotomy and CTT with MMC had similar outcomes. However, due to limitations of sample sizes, it remains inconclusive as which procedure is preferable.[17]

The horizontal corneal diameter (HCD) is typically increased in PCG patients, which serves as an indication for disease severity and a key factor for surgery selection.[18] In general, angle surgeries are recommended for PCG with an HCD <12 mm.[8] Trabeculectomy or CTT with or without the use of MMC is usually chosen for advanced cases with an HCD exceeding 14 mm.[7,19] For moderate PCG with an HCD of 12-14 mm, trabeculotomy and CTT are the two major surgical options. However, it remains unknown whether trabeculotomy, when compared to CTT, yields comparable results and fewer postoperative complications in PCG with an HCD of 12-14 mm. Therefore, we design a study to determine whether the clinical outcomes of trabeculotomy are noninferior to

those of CTT for PCG with an HCD of 12-14 mm.

Study objectives

The primary outcome of our study is to compare the 3-year success rate in lowering IOP between trabeculotomy and CTT in patients with PCG with an HCD of 12-14 mm. The secondary outcome is to assess changes in IOP and the morphometric parameters of the eyeball, visual outcomes and postoperative complications in these two surgical procedures.

METHODS AND ANALYSIS

This protocol is developed in line with the Standard Protocol Items Recommendations for Interventional Trails (SPIRIT). The SPIRIT checklist for the protocol is available as 'supplement'. The trail was registered at the Chinese Clinical Trail Registry (www.Chictr.org.cn) on 20, November 2014 with a trial identification of ChiCTR-IOR-14005588. Protocol of this trial was approved on 25 August 2014.

Trial design and setting

This study is a 3-year, prospective, randomized, single-center, noninferiority trial comparing clinical outcomes and postoperative complications between trabeculotomy and CTT in treating PCG with an HCD of 12- 14 mm. Eligible patients will be enrolled and randomly assigned to receive either trabeculotomy or CTT (figure 1). The trial is being conducted at the Zhongshan Ophthalmic Center, Guangzhou, China.

Participant selection

Inclusion criteria

Participants will be included if they meet all of the following criteria: (1) diagnosis of PCG in either eye, (2) equal to or under 3 years of age, (3) HCD between 12 and 14 mm, and (4) no previous intraocular surgery or laser treatment.

PCG is defined as follows:[20]

1. Age ≤ 3 years old.
2. IOP >21 mmHg.
3. Absence of other ocular or systemic diseases.
4. Combined with one or more of the following clinical signs: (1) corneal findings: Haab's striae, corneal edema, corneal diameters >11 mm in the newborns, >12mm in children younger than 1 year old, and >13mm in children older than 1 year old; (2) increased (>0.3) or asymmetric (>0.2) C/D ratio; and (3) abnormally increased axial length (AL).

Normal AL is as follows: 3 mo-3yrs: 19-22 mm.[21]

Only one eye per patient will be enrolled. If both eyes of a patient are eligible for the study, the eye with the higher baseline IOP will be selected. The treatment for the fellow eye will be determined at the physician's discretion.

Exclusion criteria

Patients will be excluded if they meet any of the following criteria:

- Inability of the patients' legal guardian to give informed consent.
- Inability of the patient to return to the clinic for the scheduled study visits.
- Contraindications to anesthesia or surgery for ocular disease.
- Severe corneal cloudiness precluding anterior chamber visualization.
- Secondary congenital glaucoma.
- Other coexisting ocular diseases such as an abnormal cornea, congenital iris abnormality, congenital cataract, or retinopathy of prematurity.

Withdrawal criteria

1. Failure to locate or dissect Schlemm's canal by 120°.
2. The presence of any of the following issues during the operation: severe anesthesia accident, suprachoroidal hemorrhage, or a change in the operative procedure according to the patient's condition.
3. A desire to quit the trial.

The withdrawal criteria described above have been established to ensure that the outcomes of the two procedures (trabeculotomy and CTT) will be effectively analyzed for the full 3-year duration of the study.

Interventions

All surgeries will be performed under general anesthesia by 3 attending

surgeons (XL, MBY, and MKL) who specialized in both types of surgery.

Trabeculotomy

This technique has been previously described.[8] In brief, a superior quadrant fornix-based flap will be created. A 3-mm × 3-mm superficial (12 o'clock) scleral flap of three-quarters thickness will be made. A 2-mm radial incision will be made starting from the gray zone up to the white zone, followed by entering Schlemm's canal externally. An incision will be slowly deepened until the outer wall of Schlemm's canal is opened and seeping aqueous humor is observed. Schlemm's canal will be dissected by 120° in both directions using a trabeculotome probe. The scleral flap will then be replaced with three interrupted 10-0 nylon sutures. The conjunctival flap will also be replaced with 8-0 absorbable sutures.

CTT

In the superior quadrant, CTT with MMC will be performed. A fornix-based conjunctival flap will be dissected. After dissection of a superficial (12 o'clock) scleral flap measuring 4 × 3 mm^2, MMC (0.3 mg/ ml) soaked pieces of microsponge will be applied under the scleral flap and the conjunctiva for 3 min, and the area will then be washed thoroughly with 30 ml of balanced salt solution. Then, trabeculotomy will be performed as described above. Trabeculectomy will be performed by cutting a 1-mm × 2-mm deep scleral flap, followed by a peripheral iridectomy. The scleral flap and conjunctiva will then be replaced.

Finally, the anterior chamber will be reformed with balanced salt solution.

Intraoperative data, including the duration of surgery, the same doses and duration of MMC used during the operation, anesthesia accidents, intraoperative complications, such as hyphema, iris/vitreous damage, and trabeculotomy-related problems, such as failure to identify Schlemm's canal or an inability to dissect Schlemm's canal by 120 degrees, will be collected.

Postoperative treatment and patient follow-up

Patients will be treated with prednisolone acetate 1% (Allergan, Parsippany-Troy Hills, NJ, USA) 6 times daily in combination with topical antibiotics (tobramycin 0.3%, s.a. ALCON-COUVREUR n.v) and pilocarpine 1% (Bausch & Lomb, Rochester, NY) 4 times daily for the first 4 weeks after the surgery.

Postoperative follow-up visits will be performed in the pediatric glaucoma clinic at Week 1, Week 2, Week 4, Month 3 and then every 3 months (±1 weeks) for 3 years. The scheduled examinations of the follow-up visits are summarized in Table 1. Chloral hydrate 10% (0.8 ml/kg, oral or rectal administration, the maximum dose is 10 ml per day) will be applied to patients not compliant for examinations.

If IOP is found to be high at a scheduled visit, topical antiglaucoma medication will be prescribed and the scheduled follow-up interval (if longer than 2 weeks) will be shortened to 2 weeks. Additional surgery will be performed if the IOP is > 21 mmHg on maximum anti-glaucoma medications (including pilocarpine 1%,

brinzolamide 1%, and latanoprost 0.005%) in two consecutive study visits.

Table 1 Scheduled examinations of follow-up visits.

Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Examination	Baseline	Procedure	1 w ± 2 d	2 w ± 2 d	1 m ± 7 d	3 m ± 7 d	6 m ± 7 d	9 m ± 7 d	12 m ± 7 d	15 m ± 7 d	18 m ± 7 d	21 m ± 7 d	24 m ± 7 d	27 m ± 7 d	30 m ± 7 d	33 m ± 7 d	36 m ± 7 d
Informed consent	×																
Demographic data	×																
Medical history	×																
Physical examination	×																
IOP	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
AL	×					×	×		×		×		×		×		×
HCD	×	×			×	×	×	×	×	×	×	×	×	×	×	×	×
Slit lamp examination	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Fundus photography&	×					×	×		×		×		×		×		×
B-scan ultrasound*	×					×	×		×		×		×		×		×
Refraction&	×					×	×		×		×		×		×		×

VA	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
Corneal transparency	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
CCT	×															×
Medications	×		×	×	×	×	×	×	×	×	×	×	×	×	×	×
Adverse events		×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Reoperation					×	×	×	×	×	×	×	×	×	×	×	×

In the event of nonvisibility of the fundus, & fundus photography and refraction will not be performed; *B-scan ultrasound will be used to measure cupping. IOP, intraocular pressure; AL, axial length; HCD, horizontal corneal diameter; VA, visual acuity; CCT, central corneal thickness.

Outcome assessment

Primary outcome

The primary outcome is the success rate in lowering IOP at 3 years after surgery. Success is defined as:

1. IOP≥ 5 mmHg and ≤ 21 mmHg on two consecutive follow-up visits with or without anti-glaucoma medications.[5, 22]

2. The absence of severe vision-threatening postoperative complications, such as suprachoroidal hemorrhage, retinal detachment or endophthalmitis.

3. No need for additional surgical intervention to control the IOP.

Complete success is defined as meeting success criteria without the need for anti-glaucoma medications. Qualified success is defined as meeting success criteria with the use of anti-glaucoma medications.

Secondary outcomes

The secondary outcomes will be evaluated by IOP reduction and changes in the morphometric and functional parameters of eyeball: HCD, corneal transparency, CCT, C/D ratio, AL, VA, and refraction. Postoperative complications, including hyphema, shallow anterior chamber, hypotony, surgery-related iridodialysis, complicated cataract, retinal or choroidal detachment, bleb complications (leakage or infection) and endophthalmitis, will be evaluated and recorded.

Sample size calculation

The sample calculation was based on the hypothesis that the 3-year success rate of trabeculotomy will be noninferior to that of CTT. Published studies have shown that the success rate at the 3rd year after CTT ranges from 72.6% to 87%.[1,9,23,24] We assume that the 3-year success rate of CTT will be approximately 80%. Therefore, 224 subjects (112 per group) will be needed to provide the trial with a power of at least 80% to demonstrate the noninferiority (-15% margin) of trabeculotomy to CTT (one-sided α value: 0.025). Assuming a 10% loss to follow-up, a sample size of 248 participants is required for this study, with 124 participants in each group.

Patient recruitment and baseline data collection

All subjects will first be assessed for potential participation in the study by the primary investigator. Patients who gave consent to the study will be invited to undergo enrollment examinations to determine enrollment status.

Examinations

IOP. IOP will be measured with a Tono-Pen Avia (Reichart, Depew, New York, USA) under sedation with chloral hydrate 10% and topical anesthesia. Although the use of anesthetic agents during examination under anesthesia (EUA) may influence IOP and affect the accuracy of IOP documentation, chloral hydrate has been shown to have a minimal effect on IOP in pediatric ophthalmic examinations.[18]

Slit-lamp examination. The condition of the anterior segment, including corneal clarity, corneal edema, Haab's striae, anterior chamber depth, iris, pupil, and lens, will be evaluated using a hand-held slit lamp (Keeler, Bucks, England).

Corneal clarity will be recorded as mild (iris texture clearly seen), moderate (iris seen but texture not clearly visible), and severe (iris not visible).

HCD. A caliper will be used to measure the HCD (white to white) by ophthalmologists. Participants with an HCD less than 12 mm or greater than 14 mm will be excluded.

Central corneal thickness (CCT). CCT will be measured using ultrasound pachymetry (IOPac, Heidelberg Engineering, Heidelberg, Germany). Topical anesthetic will be used prior to the application of the ultrasonic probe to the corneal surface. All measurements were taken with the child in the supine position. Ten measurements will be taken for each eye, and the lowest reading will be recorded.

C/D ratio. The C/D ratio will be evaluated using direct ophthalmoscopy (66 Vision, Suzhou, China) as permitted by the media clarity. Images showing the C/D ratio will be obtained using a hand-held retinal camera (Kowanonmyd a-D III; KowaOptimedInc, Aichi, Japan) through a dilated pupil. For children with hazy media, whose fundus cannot be visualized, fundus photography will not be performed, and a B-scan ultrasound (Quantel Medical, CF, France) will be used to rule out any intraocular pathology and to detect excavation of the optic

nerve head.

Ocular biometry. Ocular biometry, including AL, anterior chamber depth, lens thickness, and vitreous chamber depth, will be measured using A-scan ultrasound (Quantel Medical, CF, France). Ten repeated measurements will be taken and averaged for analysis.

Visual acuity (VA). VA will be measured using suitable procedures. Teller acuity cards (Vistech Consultants, Inc. Dayton, OH, USA) will be utilized at a distance of 55 cm in nonverbal children. The Lea symbols (Precision Vision, La Salle, IL) with a test distance of 3 meters and the Early Treatment of Diabetic Retinopathy Study (ETDRS) LogMAR E chart (Precision Vision, Villa Park, Illinois, USA) with a test distance of 4 meters will be employed for verbal children. Monocular VA will be assessed in the right eye followed by the left eye. For children who cannot complete the quantified VA examinations mentioned above, the ability to fix and follow light will be evaluated.

Refractive error. Refraction will be measured by retinoscopy after cycloplegia. Cycloplegia will be induced with two drops of cyclopentolate 1% instilled 5 min apart, with a third drop administered after 20 min. Cycloplegia will be then evaluated after an additional 15 min. Cycloplegia is considered complete if the pupil dilates to ≥ 6 mm and a light reflex is absent.[25] Refractive error will not be evaluated when attempts to improve the view were not successful.

All ophthalmological examinations described above will be performed in both

eyes. Chloral hydrate 10% will be applied to patients not compliant for examinations.

Written informed consent will be collected from each eligible participant's legal guardian prior to inclusion in the study. For eligible participants, demographic data (sex, date of birth, and laterality), family history of PCG and medical history (age of onset, initial syndrome, age at diagnosis, and medical treatment) will be recorded. Pregnancy and delivery information (gestational weeks, delivery mode, maternal drug intake and infection during pregnancy) will also be ascertained and recorded.

Randomization

A randomization list was generated with the SAS V 9.3 software package (SAS Institute, Cary, NC, USA) by a biostatistician who will not participate in data management. The 1:1 randomization procedure will be performed using varying block sizes. To ensure concealment, the block size will not be disclosed. The allocation of patients will be concealed using sequentially numbered, opaque sealed envelopes. A total of 248 envelopes will be prepared by two researchers not involved in the study. For each recruited patient, his/her group assignment will be revealed in the operating room on the day of surgery. Surgical management and intraoperative data will be collected.

Postoperative follow-up will be performed by investigators who will not participate in patient care and are trained to follow-up patients prior to the study.

The surgeon(s) and investigator(s) will not communicate with each other while collecting data.

Data management and monitoring

All data collected at the scheduled follow-up visits (Table 1) will be recorded in the case report forms and entered into a digital database by trained researchers. The soft copies of digital data will be stored in these devices and then in a server at the end of each visit day. The completed case report forms and hardcopy data forms will be kept in locked cabinets in the research center. The implementation of the trial will be monitored by the principal investigator. Access to the final dataset will be limited to the trial administrator and the statistician.

Statistical analysis

All statistical analyses will be performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables conformed to the normal distribution will be expressed as the mean (SD). Dichotomous and nominal variables will be expressed as frequencies, ordinal and discrete variables as median and IQR.

The primary analysis will be based on the principle of intention-to-treat (ITT) and will include all subjects who underwent randomization, with data censored at the last schedule visit. We will perform a sensitivity analysis of the post hoc worst-case scenario, in which subjects who did not complete follow-up were considered failed outcomes, and a sensitivity analysis of a post hoc complete-

case scenario, in which only subjects who had complete data all through the trail will be included. We calculated 95% confidence interval for the estimates of the absolute differences between the two treatment groups regarding the 3-year success rate using the Cochran-Mantel-Haenszel method. Noninferiority would be met if the lower limit of the 95% CI of the absolute difference did not cross the prespecified noninferiority margin (-15%). The survival data (time-to-IOP controlled) will be analyzed using the Kaplan-Meier method. The log-rank test will be employed to compare curves in the trabeculotomy and CTT groups.

Secondary outcomes will be assessed with two-sided tests. Comparisons of continuous variables distributed normally, such as the IOP, HCD, AL, and CCT will be performed between the two groups using Student's t-test. Considering that the normal IOP in children is lower than that of adults, we will use 18mmHg as a cut-off and compare the surgical outcomes between two groups after 3 years of follow-up using Kaplan-Meier method. For continuous variables not distributed normally and for discrete variables (including the C/D ratio, number of anti-glaucoma drugs, and distribution of refractive errors) between the two groups comparison will be performed using Mann-Whitney U test. The Chi-square test or Fisher's exact test will be used to compare the proportions of the visual outcomes, and complications between the two surgical groups.

Safety consideration

The safety evaluations of the study will include complications associated with surgeries as well as drugs adverse events. The procedures and drugs used in the study are routinely administered in daily practice. Thus, the trial has risks not exceeding usual clinical care that the patients would otherwise receive. Throughout the study, all adverse events will be recorded and managed.

Drug-related complications include unanticipated events caused by cycloplegia, anti-glaucoma drugs, and chloral hydrate. Dilation will be established following a slit lamp examination. Doctors will closely monitor the patients' pupil reflexes and vital signs after administering the medications.

Vision-threatening complications, such as suprachoroidal hemorrhage, retinal detachment, and endophthalmitis, will constitute major adverse events.

Trial status

Recruitment began in the first quarter of 2015. Currently, 75% of the sample size has been attained. it is anticipated that the study will reach the recruitment target of 248 participants by the fourth quarter of 2019. There are no plans for interim analysis.

PATIENT AND PUBLIC INVOLVEMENT

Patients and public were not involved in the design of the study.

ETHICS AND DISSEMINATION

This study was approved by the ethics committee of Zhongshan Ophthalmic

Center (reference number 2014MEKY023). The study protocol was also reviewed by the "5010 Plan" evaluation committee at Sun Yat-sen University, Guangzhou, China. Every year, the evaluation committee will examine the study progress and its adherence to the study protocol. Any important modifications to the protocol will be documented in the study protocol as formal amendments. These amendments will be submitted to the ethics committee of Zhongshan Ophthalmic Center and the "5010 Plan" evaluation committee of the Sun Yat-sen University for a review. The project leader will ensure that this study is conducted in accordance with the principles of the World Medical Association Declaration of Helsinki.

The study results will be presented at national and international meetings on ophthalmology.

DISCUSSION

This is a prospective, randomized, controlled intervention trial aims to provide evidence for clinicians for to better judgement regarding surgical options for patients with PCG. To the best of our knowledge, this trial is the largest clinical trial in the field of pediatric glaucoma. The findings are expected to provide evidence indicating whether trabeculotomy is noninferior to CTT in treating PCG with an HCD of 12-14 mm.

For PCG with an HCD less than 12 mm, the anatomic abnormality of Schlemm's canal is usually not significant, facilitating its identification during the

operation. As a result, angle surgery alone is sufficient to lower IOP in these patients. Sampaolesi et al[26] proposed that trabeculotomy is suitable for children with PCG in whom the corneal diameter is less than13 mm and the AL is less than 23 mm. Advanced PCG with an HCD greater than 14 mm is usually associated with a significant anatomic anomaly of the anterior drainage angle. The abnormally stretched anatomy of the limbus in these patients frequently makes it difficult to clearly identify the lumen of Schlemm's canal that has to be cannulated for the trabeculotomy. Thus, the success rate of trabeculotomy is lower in advanced PCG cases. Quigley *et al*[27] reported the results of trabeculotomy in 28 eyes with congenital glaucoma. The success rate in eyes with an HCD greater than 14 mm was 67% compared with 100% in eyes with a smaller HCD. Both of the conditions described above will lead to biases in the results. Moreover, most PCG cases in China have an HCD ranging from 12 mm to 14 mm,[7,28] and these patients have a good chance of preserving useful VA if treated correctly.

No unified guideline is currently available to determine PCG severity based on corneal diameter. Cronemberger et al[29] confirmed that a higher HCD will trigger higher HCD and AL at final follow-up. Kiskis *et al*[30] studied the HCD and AL in PCG patients and concluded that HCD measurement was a more reliable guide than AL in the assessment of PCG. Currently, we are unaware of any studies that compared long-term outcomes between CTT and trabeculotomy in PCG patients who exhibited homogeneity in terms of disease

severity. After considering the above information, we selected an HCD of 12-14 mm as an inclusion criterion. However, selection of surgical methods for the treatment of PCG and the evaluation of PCG severity based on HCD alone are issues requiring further investigation and improvement.

With regard to IOP, we selected an IOP value of ≤ 21 mmHg as a success criterion based on the previous reports.[5, 23, 31] In this study, IOP will be measured with Tono-pen which has been widely used in clinic for many years. We chose Tono-pen as the measurement by referring to the previous studies.[32-34] On the other hand, Tono-pen is particularly useful with corneal scars or edema,[35] which are often seen in PCG eyes. We used Tono-pen for all patients at each scheduled visit, which eliminated any possibility of bias due to the use of different tonometry techniques in different patients.

In conclusion, this is a large clinical trial aiming to provide evidence for the optimum first-line surgery for patients with PCG with an HCD of 12-14 mm. If the trabeculotomy group is associated with comparable surgical success and fewer postoperative complications compared with CTT group, trabeculotomy should be recommended as a primary surgical treatment for PCG with an HCD of 12-14 mm, saving trabeculectomy for future intervention. In addition, complications associated with trabeculectomy will be reduced. The visual outcome in this trial may help provide insight into the effects of surgical methods on VA. The findings of our study are expected to provide guidance to clinicians weighing the benefit and risk of trabeculotomy compared to CTT for the

treatment of PCG.

Acknowledgments

We would like to thank all of the research assistants and nursing staff involved in this trial for contributing to the practical organization and execution of this study.

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Author Contributions XL conceived the study and is the project leader for the trial. XL, XXG, YFY, JJH, YMZ, XXC, JlH and LF participated in the study design and recruited the patients. LF wrote the manuscript. XL, XXG, YTZ, and XYX critically revised the manuscript. JZ designed the database system and performed the statistics-related design. All authors read and approved the final manuscript.

Funding statement This study was supported by the Sun Yat-Sen University

Clinical Research 5010 Program (2014016) and the National Natural Science Foundation of China (81800879). The sponsor had no role in the protocol design or conduct of this study.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was approved by the ethics committee of Zhongshan Ophthalmic Center (reference number 2014MEKY023). The study protocol was also reviewed by the "5010 Plan" evaluation committee at Sun Yat-sen University, Guangzhou, China.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data available.

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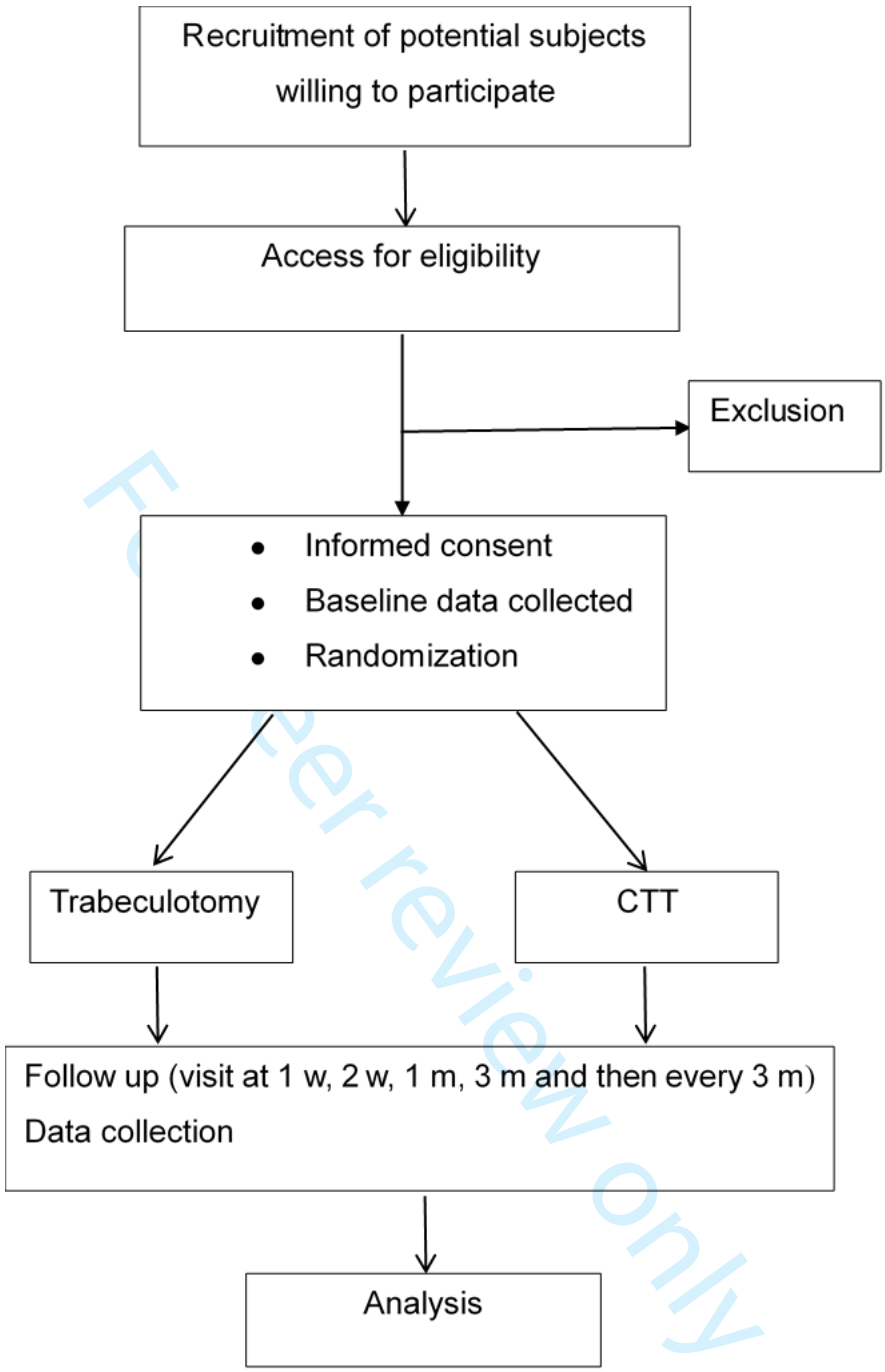
Figure Legend

Figure 1 Flowchart of the study. CTT, combined trabeculotomy-trabeculectomy.



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,24-25

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1,25
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	6

		obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10, Table1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	18
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	18
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	18
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	18
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	15-18, Table1

		protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22
Auditing	#23	Frequency and procedures for auditing trial conduct, if	21

		any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21-22
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	25

authorship		professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A