Clinical Ophthalmology

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STUDY PROTOCOL

Comparison of Subconjunctival Triamcinolone with Topical Prednisolone for Routine Anti-Inflammatory Prophylaxis in Manual Small Incision Cataract Surgery: A Single-Center, Randomized Controlled Trial Pilot Protocol

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Background: Cataract surgery is the most commonly performed operation worldwide. Prophylaxis against postoperative endophthalmitis and inflammation currently includes perioperative, patient-administered instillation of topical antibiotic and anti-inflammatory drops in the US, Europe and Latin America. As patients can face challenges with adherence to topical drops for self-instillation, injected drugs may offer a solution. Intracameral antibiotic injection is superior to drops for endophthalmitis prevention in manual small incision surgery (MSICS) and phacoemulsification eyes. Subconjunctival injection of triamcinolone acetonide (TA) is an effective method to prevent postoperative inflammation in phacoemulsification eyes. MSICS may be associated with more tissue trauma because of the larger incision size and iris manipulation. As there are no studies to date comparing injection prophylaxis with topical drops in MSICS eyes for postoperative inflammation prevention, this pilot study aims to elucidate the safety of the injection technique in this method of cataract surgery.

Methods/Design: This is a single-center, partially-masked, pilot randomized controlled trial of two groups undergoing uncomplicated MSICS. Group 1 consists of a single eye of 50 patients treated with the standard postoperative topical drops, prednisolone acetate (PA) 1%, starting four times a day in the first week tapering by one drop per week over 4 weeks. Group 2 consists of a single eye of 50 patients injected with 0.4mL of TA subconjunctivally at the conclusion of MSICS. Intracameral moxifloxacin 0.15% is injected at the end of surgery in both groups. Postop measurements are taken on day 2, and at weeks 6 and 12. The primary outcome, a safety measure, is mean intraocular pressure (IOP). Secondary outcomes, effectiveness measures, include corrected distance visual acuity (CDVA), anterior chamber inflammation, corneal and macular edema (ME).

Discussion: The objective of this study is to evaluate the safety and efficacy of a single subconjunctival TA injection compared to standard postoperative topical therapy using PA 1% in eyes undergoing MSICS.

Trial Details: Clinicaltrials.gov: NCT05248139; Protocol issue date: August 9, 2024; Amendment number: 02.

Plain Language Summary: Inflammation following cataract surgery can cause pain and blurred vision and may result in thickening of the central part of the retina (macula) in up to 5.5% of cases. Patients usually self-administer a combination of topical eye drops 3–6 times per day and over several weeks after surgery to prevent this. During a typical postoperative period, a patient may be required to put in more than 250 drops. Studies have shown that patients have difficulty with self-instillation leading to contamination of the eye drop tip or the eye, and abrasions of the eye. Patients may forget to instill doses or stop the drops prematurely. A study published in 2014 showed that more than 90% of patients were unable to instill eye drops correctly after cataract surgery.

Received: 8 March 2025
Accepted: 28 May 2025
Published: 4 July 2025

This study aims to assess the safety and efficacy of a dropfree postoperative regimen that includes a painless injection of a corticosteroid medication at the end of manual small incision cataract surgery (MSICS), one of the most common types of surgery in Central and South America and in low- and middle-income countries (LMICs) throughout the world. This surgeon-administered treatment has the potential benefit of avoiding patient adherence challenges and offers assured delivery of medication to the eye, which lasts for several weeks before dissolving. Recent studies have shown superior effectiveness of the injection technique compared with topical drops in phacoemulsification surgery, a more costly procedure. This will be the first study of this technique in MSCIS.

Keywords: cystoid macular edema, intraocular pressure rise, rebound iritis, triamcinolone acetonide injection, dropfree cataract surgery

Background

Cataract is the largest contributor to global blindness in adults aged 50 years and older and is increasing in prevalence.[1] Phacoemulsification cataract surgery is most commonly performed in high-income countries. The benefits of this technique are a smaller incision and less surgically-induced astigmatism.[2] It also bears a higher capital investment and cost of consumables.[3] In low- and middle-income countries (LMICs), limited access to health services, constrained resources and low purchasing power of populations reduce potential access to corrective surgery. In these countries manual small incision cataract surgery (MSICS) is the most efficient, cost-effective technique utilizing inexpensive, readily available instrumentation.[4,5]

Adverse events following cataract surgery include endophthalmitis and macular edema (ME). While the risk of endophthalmitis is rare, it can be sight threatening. ME is one of the most common causes of reduced vision after surgery, typically occurring in approximately 1% of cases.[6,7] In 9% of ME cases, vision loss may persist for longer than 1 year.[8]

A typical prophylaxis regimen in LMICs in Central and South America consists of patient self-instillation of topical antibiotic and anti-inflammatory medications in the postoperative period to prevent endophthalmitis and ME, respectively.[9] This may include administration of up to three different eye drops four or more times per day during the 4 to 6 weeks after surgery. In high-income countries, incorrect application of topical drops may occur in up to 90% of patients who are inexperienced with eye drop instillation.[10] Contamination of the medication bottle tip and contact with the cornea or conjunctiva can occur in up to 68% of patients.[11] In a large multicenter study, there was a failure to fill prescriptions for postoperative drops by 5% of patients who had prescription insurance coverage. This was associated with a 2-fold increase in the risk of endophthalmitis.[12] In LMICs, data on adherence and accuracy of drop instillation has not been published but these may be worse in LMICs with a lower volume of topical eye medication purchases and dispensings compared with high-income countries, especially among rural populations. Because patient adherence and correct instillation is the single largest factor for drug efficacy,[13] surgeon-directed administration of medication may improve surgical outcomes.

A prophylaxis strategy of surgeon-administered injections may circumvent participant adherence challenges and improve outcomes. Intracameral injection of antibiotic surpasses the effectiveness of topical drops and is likely sufficient as stand-alone prevention for phacoemulsification and MSICS surgery.[12,14,15] For inflammation control and prevention of ME, corticosteroid injection in the subTenon space[16,17] is equivalent in effectiveness to topical anti-inflammatory drops. More recently, evidence has shown superior outcomes when triamcinolone acetonide (TA) was injected in the subconjunctival space at the conclusion of surgery.[18,19] Compared to SubTenon, the subconjunctival location has the advantage of direct visualization of the needle tip during injection, reducing risk of globe perforation, and an easily identifiable depot for excision in the event of high IOP.[20] A large observational multicenter study demonstrated superior safety and effectiveness of a 4 mg dose of subconjunctival TA (Kenalog10 mg/mL) compared with topical prednisolone with or without topical non-steroidal anti-inflammatory drug (NSAID) in participants who underwent phacoemulsification.[20]

There are no studies to date comparing safety and effectiveness of long-acting steroid injection with topical anti-inflammatory prophylaxis in MSICS. MSICS may be associated with more tissue trauma because of the larger incision size and iris manipulation.[21,22] In a comparison of postoperative macular thickness in randomized participants undergoing MSICS and phacoemulsification and treated postoperatively with topical prednisolone, a small but statistical increase in central subfield mean thickness on spectral domain optical coherence tomography (SD-OCT) was demonstrated in the manual surgery group, though no cases of clinical ME were found in either group along with no statistical differences in visual acuity.[21] The

authors hypothesize that the difference in macular thickness was likely due to increased postoperative inflammation in the MSICS group which may have resulted from more tissue trauma because of the larger incision size and more iris manipulation inherent in the manual technique compared with phacoemulsification. Similar findings were demonstrated in another, smaller study from India, showing a small but statistical increase in macular thickness on SD-OCT in the manual group, though there were no cases of cystic spaces on SD-OCT or clinical changes on exam.[23]

This prospective, partially masked, randomized control trial will compare subconjunctival injection of 4 mg TA 10 mg/mL (Tamceton) with postoperative self-administered prednisolone acetate (PA) 1%, tapered over a 4-week period in participants undergoing MSICS in Guatemala. The primary outcome, related to safety, is the group mean intraocular pressure (IOP) and cumulative incidence of suprathreshold postoperative IOPs measured at 6 weeks. IOP rise is the most common adverse event following low dose periocular injection of corticosteroid,[20] peaking at 6 weeks following the dose.[24] Secondary outcomes, related to effectiveness, include corrected distance visual acuity (CDVA), incidence of ME and other measures of postoperative inflammation at the same postoperative intervals.

The potential benefits of surgeon-directed administration of antibiotic and anti-inflammatory drugs includes assured delivery of drug and decreased risk of endophthalmitis and ME. The benefit may be even more evident in LMICs, where access to care sites may be limited and wound contamination may be an issue.

Methods

Participants, Interventions and Outcomes

Objectives

The primary aim is to compare the safety of subconjunctival steroid injection with conventional postoperative therapy using anti-inflammatory steroid drops in patients undergoing MSICS. The secondary aim is to compare measures of effectiveness between these two regimens. The project includes: 1) an initial pilot phase establishing enrollment potential, confirming safety and feasibility of the intervention and trial; 2) the refinement of study procedures and sample size calculations for a full-scale randomized controlled trial informed by the pilot; and 3) a full trial to determine safety, efficacy, and patient satisfaction of corticosteroid injection compared with standard drops after MSICS.

We hypothesize that subconjunctival injection of 4 mg TA 10 mg/mL will result in a lower mean IOP (superior safety) and lower postoperative inflammatory measures (superior effectiveness) compared with the conventional topical steroid regimen. Here we present the protocol for Phase 1 which includes the pilot trial.

Trial Design

Phase 1 is a single-center, randomized, partially masked pilot study and is a proof of concept for subconjunctival TA injection in MSICS based on previous smaller studies[18,25] and a large observational study in phacoemulsification patients.[20] The protocol is consistent with the SPIRIT 2013 statement.[26] A completed SPIRIT checklist for this study is available in the supplementary material (Figure S1). Patients undergoing uncomplicated MSICS are randomized in a 1:1 fashion to two groups: group 1 (conventional treatment arm) includes 50 eyes of 50 participants who self-administer a weekly tapering dose of PA 1% for 4 weeks, and group 2 (intervention arm) includes 50 eyes of 50 participants injected with 4 mg TA 10 mg/mL at the conclusion of surgery. No eye drop medications are instilled in the postoperative period in group 2. All participants have outcomes monitored at day 2, week 6, and week 12.

Study Setting

Guatemala is the largest economy in Central America and is classified as a middle-income country.[27] Visualiza is a community clinic in Guatemala City serving self-pay and subsidized care patients. Eligible participants in this study are drawn from the social, subsidized clinic population.

Eligibility Criteria

Inclusion Criteria

- Participants of any gender
- Ages 50 to 85 years at the time of allocation

https://doi.org/10.2147/OPTH.S527039

- Significant cataract by the LOCS III classification
- Snellen CDVA 20/40 or worse
- Axial length of 20.1 mm to 25.9 mm by immersion biometry
- IOP less than 21 mmHg by Goldmann tonometry
- Corneal thickness less than 600 microns by pachymetry
- Signed informed consent form

Exclusion Criteria

- Treatment with a topical or systemic steroid drug up to 3 months prior to surgery
- Morgagnian cataract
- Ocular comorbidity including corneal abnormalities, retinal disease, glaucoma, ocular hypertension, history of uveitis, pseudoexfoliation syndrome, history of steroid response, traumatic cataract, subluxated lens, ME or endophthalmitis
- Random glucose result greater than 200 mg/dL by point of care testing
- Uncontrolled arterial hypertension or blood pressure during screening ≥ 160/80
- Intraoperative complications: posterior capsular rupture, iris prolapse, zonular dialysis, vitreous loss, iris trauma or Descemet's detachment.

Interventions

All participants undergo MSICS and intraocular lens (IOL) placement (Appalens, Appasamy, India) by a single surgeon with the same intraoperative medications including viscoelastic (Appavisc PFS, Appasamy, India) and, following stromal hydration of the wounds at the conclusion of surgery, intracameral injection of 0.5 mL moxifloxacin 0.15%. This concentration is achieved by aseptically mixing 0.3 mL Vigamox 0.5% (Novartis, Spain) with 0.7mL of balanced salt solution (BSS). Preservative-free carmellose 0.5% is dispensed to all participants for instillation as needed as a lubricant for symptoms consistent with dry eye. Participants in both groups receive no topical or systemic antibiotic or anti-inflammatory medications in the preoperative period.

Participants in group 1 are instructed to begin self-administered topical PA 1% (Prednefrin Forte, Allergan, Argentina) four times daily beginning on the first postoperative day and tapering by one drop per day at the beginning of each subsequent week for a total of 4 weeks of instillation. Group 2 participants receive a subconjunctival injection of 0.4 mL TA 10 mg/mL (Tamceton, Hanall Biopharma, Korea), a dose of 4 mg, placed 6 mm inferior to the inferior limbus. Topical antibiotics, corticosteroid or NSAIDs are not prescribed for preoperative or postoperative administration for any participant in any group.

Any form of additional corticosteroid administration or ophthalmic medications by any route other than by protocol is prohibited.

Outcomes

The primary outcome is the mean IOP by group at 6 weeks measured by Goldmann applanation as a measure of safety following steroid injection. The masked ophthalmologist obtains three IOP measurements at each visit and the median value will be used for analysis at all time points.

Secondary outcomes

- Mean IOP by group at 12 weeks measured by Goldmann applanation
- Proportion of IOP instances of 30 mmHg or greater at day 2, and at weeks 6 and 12
- CDVA at 6 and 12 weeks measured at 6 meters with Snellen chart
- Slit lamp anterior chamber (AC) inflammation score at 6 and 12 weeks[28] (Table 1)
  - Score = grade cells + grade flare
- Proportion of participants with AC inflammation score of 5 or more in each group.

Table 1 Scoring of Anterior Chamber Inflammation

Grade	Cells/field	Flare Description
0	< 1	No flare
0.5+	1–5	–
1+	6–15	Faint
2+	16–25	Mild - iris details are clear
3+	26–50	Moderate - iris details are hazy
4+	> 50	Severe - presence of fibrin

Notes: Field size is a 1 mm by 1 mm slit beam; there is no 0.5+ score attributed for flare.

- Subconjunctival hemorrhage presence and size at day 2, and at weeks 6 and 12
- Proportion of participants with grade 3 corneal edema in each group at 6 and 12 weeks[29] (Table 2)
- Proportion of confirmed ME cases in each group
- Proportion of endophthalmitis cases in each group
- Proportion of any other adverse events and reactions in each group.

Participant Timeline

Day 1 – Screening and Recruitment

Potential participants are evaluated by a masked ophthalmologist by collecting the following:

- Demographic information
- CDVA
- IOP
- Ophthalmic exam of anterior and posterior segments
- Corneal pachymetry (iPac, Reichert AMETEK, USA)
- Immersion biometry (A-Scan PLUS model 24–4400, Accutome, KEELER, USA)

Upon meeting criteria, the evaluating ophthalmologist provides information related to the risks, benefits and alternatives of no surgery, surgery with standard prophylaxis and surgery with the intervention prophylaxis. Information is presented verbally and in writing, in plain, simple Spanish language. All participant questions are thoroughly answered.

Patient and eligibility data are entered into a REDCap[30,31] (Figure S2) database and a unique identification code assigned. Following a complete discussion, patients who agree to participate sign the informed consent form (Figure S3).

Table 2 Corneal Inflammation Grading Based on Slit Lamp Corneal Clarity

Grade	Description
0	No corneal edema
1	Iris details visible
2	Pupillary margin visible, iris details not visible
3	Pupillary margin not visible
4	Cornea totally opaque

https://doi.org/10.2147/OPTH.S527039

The participant may revoke consent at any time without penalty or loss of benefits for which they would be entitled and will not affect the activities performed or data obtained prior to the withdrawal of consent for further participation.

At the completion of complication-free surgery on the same day, randomization occurs and the participant is assigned to control group 1 or intervention group 2. An unmasked ophthalmologist explains the topical drop schedule (group 1) and schedules follow up appointments (both groups). Table 3 summarizes the examination schedule.

Day 2: First Postop Visit

A masked ophthalmologist performs biomicroscopy in the clinic at the first postoperative visit. Examination data are entered into REDCap and includes the following core elements:

- IOP measurement by Goldmann tonometry
- Presence of subconjunctival hemorrhage
- Corneal edema grade
- Anterior chamber cell and flare score
- Any symptoms or signs which could be grouped as an adverse event

Uncorrected distance visual acuity is also obtained and recorded. An unmasked ophthalmologist performs the following core elements:

- Records adherence to topical regimen (group 1)
- Measurement of subconjunctival depot diameter (group 2)
- Explains topical drop schedule (group 1)
- Schedules follow up appointments (both groups)

The timing of this visit can be between day 2 and day 4.

Week 6: Second Postop Visit

The core data elements above are performed plus a CDVA and a macular/retinal examination by the masked ophthalmologist. Data are entered into REDCap. The timing of this visit is day 43 ± 2 days after surgery.

Week 12: Third Postop Visit

The same data as week 6 are obtained and entered into REDCap except that explanation of drop schedule (group 1) and

Table 3 Screening and Examination Schedule in This Study

Screening	Day 1 (Surgery)	Day 2	Week 6	Week 12
CDVA	X		X	X
IOP	X	X	X	X
AC and cornea exam	X	X	X	X
Dilated Retinal Exam	X		X	X
Corneal Pachymetry	X			
Axial Length	X			
Record Adverse Events	X	X	X	X
Medication Review	X	X	X	X

Abbreviations: CDVA, corrected distance visual acuity; IOP, intraocular pressure; AC, anterior chamber.

follow up scheduling are not performed for participants that have completed the study without an adverse event. For these participants, a follow up visit in 1 year is recommended by the ophthalmologist to all participants. The timing of this visit is day 85 ± 2 days after surgery.

Sample Size

Based on sample size calculation for the primary outcome, mean IOP at 6 weeks, we anticipate that inclusion of 50 patients per arm (100 eyes of 100 patients total) will provide 80% power to detect an absolute difference of 0.90 mmHg in mean IOP at week 6 between the two groups. We assumed a loss to follow-up of 10% and a mean IOP of 14.3 mmHg with a standard deviation of 1.5 mmHg in the topical prednisolone group based on previous data describing the mean IOP and range for a group of patients receiving topical prednisolone at day 28.[16] The standard deviation used for our calculation was estimated based on an approximation using the range/4.

Recruitment

Participants are recruited from the social clinic at Visualiza and informed that all costs for the procedure and post-operative care in the study protocol are paid for by the study sponsor. Participants are also informed about the evidence of safety and effectiveness of the intervention in previous phacoemulsification studies and the similarity in outcomes between phacoemulsification and MSICS with conventional prophylactic therapy.

Assignment of Interventions

At the conclusion of uneventful MSICS, and following intracameral antibiotic injection, the unmasked ophthalmologist accesses REDCap software to assign the treatment arm. Participants are randomized to treatment arms in a 1:1 ratio using a pre-generated block randomization sequence implemented by the unmasked data analyst. Blocks of sizes 4, 6, and 8 will be randomized with a 1:1 ratio within each block. The surgical team is apprised of the allocation. For participants allocated to group 2, a member of the operating team will draw up the TA for injection by the operating surgeon as the final step in surgery. PA drops are dispensed to participants in group 1 by an unmasked ophthalmologist with instructions for the postoperative regimen of administration and instillation technique.

Participants in both groups are instructed in the general care of the eye and restrictions in activity. In addition, all participants are instructed to withhold questions about any potential medication related issues during subsequent evaluation by the masked evaluating ophthalmologist. The masked evaluator is instructed not to elicit information about a participant's postoperative treatment regimen and to avoid manipulating or depressing the lower eyelid of the surgical eye which could potentially unmask the participant's allocation. External research advisors are masked throughout the enrollment and follow up period.

Masking & Investigator Roles

Each study ophthalmologist is granted access to the REDCap database according to a defined role ensuring masking throughout the study as noted below and in Table 4.

- Principal investigator (PI; masked) is the ophthalmologist responsible for providing study information, answering subject questions and completing the informed consent process, and assigning an identification code to each subject. This investigator does not have access to any data of subsequent treatment including surgery or follow ups.
- Preoperative evaluation ophthalmologist (masked) is responsible for reviewing eligibility criteria, collecting demographic characteristics and performing preoperative measurements (CDVA, axial length, baseline IOP, corneal thickness, dilated ophthalmoscopic exam) prior to cataract surgery. This investigator has access to the preoperative REDCap form only.
- Surgeon ophthalmologist (unmasked) does not participate in preop or postoperative examinations and does not have access to REDCap.
- Randomizing ophthalmologist (unmasked) is responsible for randomization and allocation of participants upon completion of uncomplicated MSICS, entering surgical information into the REDCap surgical form, and for explaining the

Table 4 Investigator Roles

ROLE	Day 1 (Preop, Surgery)	Day 2	Week 6	Week 12
Principal Investigator (Masked)	Assigns participant ID	Administration	Administration	Administration
Preop Evaluating Oph (Masked)	Preop exam, checks eligibility	X	X	X
Surgeon Oph (Unmasked)	Surgery	X	X	X
Randomizing Oph 1 (Unmasked)	Randomization	X	X	X
Postop Evaluating Oph (Masked)	X	Examination	Examination	Examination
Postop Evaluating Oph (Unmasked)	X	Adherence, depot exam, scheduling	Adherence, depot exam, scheduling	Adherence, depot exam, scheduling

Abbreviations: ID, identification code; Oph, ophthalmologist.

postoperative therapeutic regimen according to the assigned group. REDCap access is limited to the surgical data entry and randomization form. This investigator is not involved in subsequent participant follow up.

- Postop evaluating ophthalmologist (masked) is responsible for performing a complete ophthalmologic evaluation and collecting postoperative variables (CDVA, IOP, degree of AC swelling, degree of corneal swelling, dilated ophthalmic examination, SD-OCT, analysis for suspected ME, complications and adverse events). This investigator has access to participant examination data in REDCap but not allocation information or postoperative examination findings related to prophylaxis medication treatment (topical adherence for group 1 and steroid depot measurements for group 2) which are recorded on a separate form by the unmasked postoperative evaluating ophthalmologist.
- Postoperative evaluating ophthalmologist (unmasked) is responsible for assessing adherence to postoperative treatment in group 1; examining the inferior bulbar surface and measuring the diameter of subconjunctival steroid deposition in group 2; and for scheduling follow-up appointments for all participants. This investigator has access to all participant examination, demographic and allocation information.

Data Collection and Management

Collection

Examination data are entered into REDCap electronic forms by each ophthalmologist with access limited according to the defined role. Forms are verified for completeness and face validity by an unmasked evaluator who then locks each form to prevent further editing.

Visual acuity is measured with a Snellen chart at a distance of 6 meters in a single room in the clinic. For data analysis, CDVA is converted to logMAR.[32] Anterior segment exam is conducted with a (Haag-Streit BI-900, Bern, Switzerland) biomicroscopic slit lamp.

Adherence to topically self-administered prophylaxis treatment in group 1 (dichotomous variable, yes/no) is determined through interview by an evaluating postoperative unmasked ophthalmologist and collected on a questionnaire (Figure S2). The evaluating ophthalmologist scores the variable as adherent when at least 75% of drops are confirmed by the participant to have been instilled. While patient self-reporting may be biased towards adherence, this is an efficient method of ascertainment and if present, would bias the results away from the superiority of safety and efficacy of the intervention (injection) rather than towards it (type II error).

The single center and single surgeon nature of this pilot study may introduce bias. The planned subsequent larger study will include multiple surgeons in different settings.

Management and Quality Control

The primary sponsor (Clínica Visualiza) is the owner and manager for the data generated in the study. Data are electronically stored in a secure, encrypted manner and will be maintained in accordance with internal and regulatory policies for a period of 5 years. REDCap is maintained on servers in the United States. Each investigator has a unique username and password and access is restricted according to role definition. Patient specific analysis is conducted on sponsor systems behind a firewall following Guatemalan privacy regulations. Deidentified analysis of data are conducted via end-to-end encrypted communication networks. The sponsor is the owner of the data generated in the study and will maintain them. Weekly masked data reports are distributed to the study team to monitor enrollment progress, data quality, and data completeness.

Statistical Analysis

Superiority analyses will be performed. A linear regression model comparing mean IOP by group at 6 weeks, including a covariate for baseline IOP, will be used for the primary analysis. Other continuous outcomes, including mean IOP at 12 weeks, CDVA (logMAR) at 6 and 12 weeks, and subconjunctival hemorrhage size, will be analyzed similarly. Binary outcomes, including IOP peaks, presence of subconjunctival hemorrhage, presence of ME, presence of corneal edema, and presence of each of serious and non-serious adverse events, will be analyzed in logistic regression models to compare each outcome by group. Model assumptions will be checked for appropriateness of the primary analysis including linearity, independence of errors, homoscedasticity, normality of residuals, and multicollinearity. Transformation of outcomes and/or predictors will be considered as indicated in the case of violations and transformation of the results will be considered when indicated. Baseline characteristics will be presented by arm. Subgroup analyses will be performed for mean IOP at 6 weeks using subgroups defined by age and preoperative IOP, in linear regression models similar to those used for the primary analysis, with the addition of a term for subgroup and an interaction term for subgroup and treatment arm. In case of missing data, the last recorded observation will be used. All analyses will be performed on an intention-to-treat basis and each outcome comparison will be considered statistically significant with an alpha value of 0.05. A per-protocol analysis will be performed including participants without obvious postoperative complications at first follow-up. 95% confidence intervals will be reported for all outcomes. P-values will be calculated using permutation. R (R Foundation for Statistical Computing, Vienna, Austria) will be used for all analyses.

Because this is a pilot study, it is anticipated that recruitment will be completed in a short period of time, therefore no interim analyses have been specified.

Monitoring

Data and Safety Monitoring Committee/Medical Monitor

The medication intervention (group 2) replicates the dose in previously published studies of phacoemulsification surgery in which no associated serious adverse events were reported. Primary and secondary outcomes in this MSICS study, consisting of clinical inflammation measures and visual acuity, should approximate those in phacoemulsification surgery.[22,23] For these reasons and the limited scope of this pilot study, a data and safety monitoring committee (DSMC) requirement was waived by the Ethics Committee.

The medical monitor, a masked consulting ophthalmologist, assesses individual adverse events and aggregated non-serious adverse events to determine if the study thresholds are met for additional review by an external body. Findings of the medical monitor will be reported to the PI.

Withdrawal and Discontinuance

A participant may withdraw from the study for any reason. Data collected prior to date of withdrawal remains a part of the study and will be analyzed.

Any of the following criteria triggers a review by the medical monitor for possible early termination of the study.

- IOP greater than 35 mmHg for 3 or more consecutive days in 3 or more participants in any group
- Anterior chamber inflammation score of 5 or more for 7 or more days in 3 or more participants in any group
- Corneal edema of grade 3 or more for 7 or more days in 3 or more participants in any group
- Confirmed ME in 3 or more participants in any group
- Confirmed endophthalmitis in 1 or more participants in any group

An ad hoc DSMC of independent content experts may be formed upon the recommendation of the medical monitor or external consultants in consultation with the PI. The composition of the committee will be determined by the PI and the medical monitor. Following review, either by the medical monitor, DSMC or both, a report of findings is submitted to the Ethics Committee with a recommendation for modification of this protocol or for early termination of the study. All participants with continued risk will continue to be monitored by the investigators and the medical monitor.

Adverse Events

Adverse events are untoward conditions in a study participant, during surgery or in the follow up period, and are either serious or non-serious. Serious adverse events include confirmed endophthalmitis and any other adverse events resulting in hospitalization, death, significant morbidity, or permanent disability. Adverse reactions and serious adverse reactions are any adverse medical event or serious medical adverse event, respectively, in a participant for whom an administered treatment medication has been determined to have a causal relationship. Causality is based on a reasonable temporal sequence from the administration of drug to the subsequent adverse event and is determined by the medical monitor.

The PI reports all serious adverse events within 24 hours of discovery to the study sponsor and the Ethics Committee. The PI will then conduct a review to assess the potential impact, including risks and benefits, on study participants and report the findings to the Ethics Committee on a timeline based on the Committee's request. Adverse reactions will be reported to the Ethics Committee within 7 days of discovery.

Defined Non-Serious Adverse Events Include

- IOP 35 mmHg or higher
- Anterior chamber inflammation score of 5 or more (cell + flare)
- Corneal edema grade 3 or higher
- Clinical ME diagnosed by CDVA of 20/40 or worse and SD-OCT evidence of central cystic spaces or central subfield thickening greater than 320μm.
- Slit lamp exam findings of a postoperative onset of scleral thinning, subconjunctival hemorrhage, IOL decentration, wound leakage, conjunctival dehiscence, cortical lenticular remnants in the anterior chamber, or hyphema.

Non-Serious Adverse Event Management

IOP

Steroid treatment, whether applied topically or by injection, incurs risk of IOP rise. This may cause subtle or significant vision loss depending on the amount and time course of IOP elevation. Treatment to lower IOP and reduce risk of vision loss consists of the step-wise addition of, first, a topical beta-blocker, second, a topical carbonic anhydrase inhibitor, and third, topical brimonidine. Triple therapy is the concurrent administration of all three topical drugs.

Initial High IOP Visit

The following management protocol applies for any visit, where an IOP measurement of 30 or above is measured for the first time:

a. A measurement of 30–34 mmHg is treated by dispensing a topical beta-blocker for twice daily self-instillation by the participant for 1 week. Follow up is scheduled for 1 week.

b. A measurement of 35–44 mmHg is treated by dispensing a topical beta-blocker and a topical carbonic anhydrase inhibitor for twice daily self-instillation beginning on the day of presentation. Follow up is scheduled every 24 hours until the IOP is 34 or less whereupon the follow up protocol guides additional treatment.
c. A measurement of 45 or greater is treated with triple topical therapy. The unmasked postoperative evaluating ophthalmologist determines the allocation group of the participant. A group 2 participant will have the option to have the visible corticosteroid depot excised or left in place. Excision is performed in clinic at the slit lamp following topical anesthesia and administration of topical phenylephrine 1%. Participants with excised depots are treated with PA four times daily for 1 week followed by a weekly taper of 1 drop per week for a total of 4 weeks of treatment. All participants are followed every 24 hours until the IOP is 34 or less whereupon the follow up protocol guides additional treatment.

Follow Up Visits

a. IOP below 21 - topical anti-hypertensive treatment is discontinued.
b. IOP 21–34 mmHg – current treatment is continued and a topical carbonic anhydrase is added or continued twice daily; follow up is scheduled for 1 week.
c. IOP of 35 or greater – triple topical therapy is continued for a total of three days. Following that, the PI determines additional treatment and submits an adverse event report to the Ethics Committee.

AC Inflammation

A participant with an inflammation score of 5 or more (cell + flare) at any visit is examined by the unmasked evaluating ophthalmologist who determines the allocation group. Participants in group 1 are treated by doubling the frequency of PA administration based on the current dosing at the time of presentation. For example, if a participant presents during week 2 with pain and blurred vision and has score of 5 (cell + flare), the PA dose would be increased from three times daily to six times daily. Tapering would proceed by 1 drop per week. Follow ups are scheduled weekly until drops are discontinued. Participants in group 2 are started initially on PA four times daily, tapering 1 drop per week for a total of 4 weeks. Follow up is scheduled weekly until drops are discontinued. In all cases, persistence of the same level or greater inflammation from one visit to the next are addressed by the PI. In cases of persistence of an inflammation score of 5 or more for 1 week, the PI will determine additional treatment and submit an adverse event report to the Ethics Committee.

Corneal Edema

A participant with grade 3 corneal edema is examined by the unmasked evaluating ophthalmologist who determines the allocation group. Treatment and reporting follow the protocol for AC inflammation above but with a threshold of grade 3 corneal edema for more than one visit and for more than one week requiring follow up by the PI and reporting to the Ethics Committee.

Clinical Macular Edema

ME is suspected in a participant with a CDVA of 20/40 or worse at the 6- or 12-week visit or with a subjective perception of visual impairment at any time during the study. Upon presentation, the unmasked evaluating ophthalmologist will obtain SD-OCT. Confirmation of clinical ME is a CDVA of 20/40 or worse and central cystic spaces or central subfield thickness of 320 μm on SD-OCT. Confirmed ME is treated with topical bromfenac 0.09% (Ocuflam MedPharma, Guatemala) twice daily for 4 weeks. Follow up is scheduled 4 weeks following presentation for ophthalmic exam and repeat SD-OCT. Persistent ME at the subsequent visit is treated with 1.0 mL of peribulbar TA 40 mg/mL (4 mg) and a follow up is scheduled for 4 weeks. Persistent ME at that second follow up visit is treated at the discretion of the consulting clinical retinal specialist. The PI will submit an adverse event report to the Ethics Committee for persistent ME for more than 6 consecutive months.

Endophthalmitis

The presence of vitritis plus any of the following: hypopyon, decreased visualization of the retina on ophthalmoscopic exam, decreased visual acuity, or ocular pain between day 3 and 14 will trigger the diagnosis of presumed endophthalmitis. Vitreous sampling for Gram's stain and culture and sensitivity are obtained followed by intravitreal injection of 0.1 mL vancomycin 10 mg/mL and 0.1 mL ceftazidime 20 mg/mL. Ancillary treatment is initiated consisting of topical moxifloxacin 0.5% every hour, oral moxifloxacin 400 mg every 24 hours for 5 days, and the patient is scheduled for follow up in 24 hours. Ancillary treatment is continued the following day for a clinical response to treatment and the patient receives continued observation every 48 hours. Lack of clinical response is addressed with vitrectomy within 48 hours. A positive culture result or subsequent serial clinical exams with a clinical picture of endophthalmitis confirms the diagnosis and the PI submits a report to the Ethics Committee.

Documentation of all adverse events, medication administration and responses to treatment is recorded in REDCap.

Modification of the Protocol

Any modifications to the protocol which may impact the conduct of the study, potential benefit of the participant or which may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects require formal amendment to the protocol. Such amendment will be agreed upon by the study investigators and advisors and approved by the Ethics Committee prior to implementation.

Administrative changes with minor corrections or clarifications that have no effect on the conduct of the study are agreed upon by study investigators and advisors and documented.

Ethics and Dissemination

The independent Ethics Committee (Zugueme, 3ra calle 11–36 zona 15, Col. Tecún Umán, Guatemala, Guatemala), is the body in Guatemala with authority to approve research plans and protocols and referred to in this study as the Ethics Committee. The study protocol, informed consent form and all documents provided to participants during enrollment and throughout the study were approved by the Ethics Committee before study activities began. All modifications to the protocol affecting care and treatment of the participant, including interventions, surgical technique, follow up periods, and medications are submitted to the Ethics Committee for approval prior to implementation.

The study is conducted under the precepts of the Declaration of Helsinki, complies with the norms of Good Clinical Practices and with the Regulations for the Regulation of Clinical Trials in Humans, Ministerial Agreement 206–2021 of the Ministry of Public Health and Social Assistance, Guatemala.

Confidentiality

The study complies with the General Data Protection Regulation (GDPR) and local Guatemalan law. Processing of personal data of participating subjects is minimized through the de-identification of participant name and demographic information for all investigators except the PI and the preop evaluating ophthalmologist.

Consent

Participants who demonstrate explicit interest in participating and are eligible will be informed verbally and in writing in simple and understandable language about the nature, duration, risks, benefits and alternatives of the proposed treatment. Participants are informed about the importance of adherence to the treatment protocol and follow up. Eligible participants will have the opportunity to ask questions about the research and clarify their doubts in a calm environment. All questions will be adequately answered to ensure that the participant has all the information required to make an informed decision about participation in the study (Figure S3).

The participant may revoke his or her consent at any time without penalty or loss of any benefits to which he or she would otherwise have been entitled and will not affect the activities performed or data obtained with the initial signature prior to the withdrawal of consent.

Financial Interests and Incentives

Investigators are employees of Visualiza Clinic in Guatemala City, a sponsor of the study. Seva Foundation, an additional sponsor, is a non-profit non-governmental organization based in Berkeley, California. There are no conflicts of interest or financial incentives for investigators or consultants/advisors in any product under investigation in this study.

Participants do not receive direct remuneration in this study. The benefits of participation include the evaluation, surgical procedure, postoperative visits and all per protocol medications at no cost. Management and care of participants with adverse events will be covered by Visualiza Clinic until resolution. There are no other provisions for ancillary or postoperative care beyond protocol. The sponsor may pay for meals and transportation for those participants living outside Guatemala City.

Dissemination of Findings

The sponsor authorizes the PI and the sub-investigators to submit to scientific publications in ophthalmologic or other related medical journals and to disseminate the results in medical conferences using aggregated, de-identified data.

Discussion

This pilot study is a proof of concept for the safety and effectiveness of injected subconjunctival TA for routine inflammation prophylaxis in MSICS. The pilot sample size and intervention are in line with other randomized controlled trials in phacoemulsification patients.[18,25] The expectation is that safety and effectiveness of injected 0.4 mL TA 10 mg/mL for inflammation prophylaxis in MSICS parallels the previous findings in phacoemulsification surgery[18,20,25] as the incidence of clinical ME in both techniques are similar.[22,23] While the primary outcome for the pilot study is a safety measure, the subsequent larger, multisurgeon trial will include effectiveness of ME prevention and postoperative inflammation reduction as measured by subfield macular thickness on SD-OCT and AC inflammation scores. The adoption of this technique, along with stand-alone intracameral antibiotic injection for infection prophylaxis, has the potential to improve clinical outcomes through the reduction of ME and postoperative inflammation[20] as well as reducing costs of the healthcare provider and to the patient,[33,34] which may be particularly beneficial in LMICs.

Abbreviations

MSICS, manual small incision cataract surgery; TA, triamcinolone acetonide; IOP, intraocular pressure; IOL, intraocular lens; LMIC, low- and middle-income countries; NSAID, non-steroidal anti-inflammatory drug; ME, macular edema; SD-OCT, spectral domain optical coherence tomography; PA, prednisolone acetate; CDVA, corrected distance visual acuity; AC, anterior chamber; PI, principal investigator.

Data Sharing Statement

Data can be available and shared upon request to the corresponding author. Additional trial details can be found in Table S1.

Ethics Approval

This study is conducted under the principles of the Declaration of Helsinki, in compliance with Good Clinical Practice standards and with the Regulations of Clinical Trials in Humans, according to the Ministerial Agreement 206-2021 of the Ministry of Public Health and Social Assistance of Guatemala. The study has been approved by the Independent Ethics Committee Zugueme, protocol number: PROZU673-24, Invest No INVZU319.12.

Consent for Publication

Participants in this study provide consent to the de-identified publication of images and data. Informed consent forms are maintained by the PI.

Acknowledgments

Gena Damento – Assistance in creating REDCap forms. Rolando Pintro – Creating the REDCap server for this project. Suzanne Gilbert – Seva consultant who was instrumental in securing the funding for this project.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Trial Sponsor: Clinica Visualiza. Contributor: Seva Foundation. Funding sources had no role in the design, execution, analysis or interpretation of the data in this study.

Disclosure

Dr Kieran O'Brien reports grants from Gates Foundation, NIH, Seva Foundation, and Fox Family Foundation, outside the submitted work. The authors have no other relevant financial or non-financial interests to disclose for this work.

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