

NCT: 02909140

PI: Fasika Woreta

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TITLE: Optimal Method for Mydriasis in Cataract Surgery

JHM IRB - eForm A – Protocol

1. Abstract

- a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Obtaining appropriate mydriasis prior to cataract surgery is an important variable in successful surgery. The current practice includes using topical anticholinergic and sympathomimetic agents in the preoperative area prior to cataract surgery, but the pupils are sometimes insufficiently dilated and can often need additional mydriasis with intracameral agents during cataract surgery. Pre-operative topical mydriatic drops take time to take effect, are mildly uncomfortable for the patient, and have a cost to the healthcare system. If intracameral mydriasis alone can achieve adequate pupil dilation, perhaps topical mydriatics would not be needed. The purpose of this study is to evaluate whether topical versus intracameral versus topical + intracameral mydriasis is the optimal way to dilate pupils during routine cataract surgery. The results of this study have implications for improving the efficiency and reducing time prior to cataract surgery. In addition, it has significant potential to reduce the cost associated with cataract surgery if preoperative drops can be eliminated.

2. Objectives

To determine the optimal method of mydriasis for routine cataract surgery, comparing preoperative topical versus intracameral versus both, measured by pupil size just prior to capsulorrhexis.

3. Background

Recent research has compared the use of intracameral and topical agents with the preoperative pupil size and cataract surgery success. Studies have compared topical mydriatics with intracameral lidocaine and found no significant difference in dilation.^{1,2} Other studies have compared topical mydriatics with intracameral dilation that includes solutions with and without epinephrine in the irrigating solution and concluded that irrigating solutions without epinephrine can safely be used with intracameral mydriatics but epinephrine is useful when using topical mydriatics.³ There have also been studies comparing the success of longer acting drug inserts of mydriatic agents with the use of intracameral agents.⁴ In addition to these standard agents, different surgeons have used various formulations of topical and intracameral agents to perform mydriasis.⁵ As of yet, there is no formal, standardized method for mydriasis and no large prospective study comparing the outcomes of the various methods. Considerations

¹ Samarai V, Haghighi N, Sharifi N. Pupil dilation with intra-cameral lidocaine versus topical midriatics during phacoemulsification. *Global Journal of Health Science* 2014;6:8-12

² Lundberg B, Behndig A. Intracameral mydriatics in phacoemulsification cataract surgery. *JCRS* 2003;29:2366-71

³ Lundberg B, Behndig A. Intracameral mydriatics in phacoemulsification surgery obviate the need for epinephrine irrigation. *Acta Ophthalmol Scan* 2007 Aug;85(5):546-50

⁴ Morgado et al Comparative study of mydriasis in cataract surgery: topical versus Mydriaserit versus intracameral mydriasis in cataract surgery. *Eu J Ophthalmol* 2010; 20 (6): 989-993

⁵ MyersWG and Shugar JK. Optimizing the intracameral dilation regimen for cataract surgery: prospective randomized comparison of 2 solutions. *JCRS* 2009;35:273-76

such as cost and time spent on preoperative mydriatic agents in light of the amount of success seen with these agents calls into question the need for such agents. We would like to study the amount of pupillary dilation seen with topical preoperative mydriatic agents compared to intracameral agents compared to the use of them both together.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

This will be a prospective randomized controlled trial. Patients will be consented and enrolled at their pre-op visit. They will be randomized to topical drops alone, intracameral injection alone, or topical plus intracameral mydriasis. All patients will receive intracameral lidocaine, as this is used for its anesthetic effect but also has some mydriatic effect. The intervention will take place on the day of the operation. Patients will be followed until post-operative month #1. This timeline is identical to the routine standard of care for cataract surgery at the Wilmer Eye Institute.

b. Study duration and number of study visits required of research participants.

Data will be gathered on 4 visits: pre-op clinic visit, day of operation, and post-operative day #1 and post-operative month #1. These are all standard visits for routine cataract surgery, and this study will not require the patient to make any extra visits. Enrollment will continue until the sample size is met.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Patients cannot be blinded to whether or not they receive topical mydriasis eye drops, and no placebo drops are necessary because patients cannot voluntarily control their pupillary constriction, so no placebo effect would be expected. The surgeon cannot be blinded to whether or not the patient has received topical mydriasis eyedrops in the pre-op area because it will be evident based upon whether or not the patient's eye is dilated. Another researcher who was not present in the operating room will grade the photographs and measure the pupil size, and this researcher will be blinded to which intervention the patient received.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Currently, routine care for cataract surgeries includes topical plus intracameral mydriasis. It is hypothesized that intracameral mydriasis alone may be sufficient to adequately dilate the pupil for cataract surgery. Patients who are not adequately dilated at the time of pupil size measurement immediately before the capsulorrhexis step will subsequently receive additional pharmacologic mydriasis, visco-dilation, or iris expansion devices to dilate their pupil to a size that is adequate for their surgery. Therefore, no matter which group the patient is in, their pupil will be eventually dilated to a size that is adequate to proceed with surgery.

e. Justification for inclusion of a placebo or non-treatment group.

There is no placebo or non-treatment group, since all patients must be somehow dilated in order to undergo cataract surgery. The purpose of this study is to compare 3 methods of dilation.

f. Definition of treatment failure or participant removal criteria.

The pupil size will be measured after the viscoelastic is injected and before the capsulorrhexis is performed. Treatment failure is defined as a pupil size that is clinically deemed too small to safely proceed with surgery (approximately less than 5 mm). At this point, a rescue intervention will be implemented with additional pharmacologic mydriasis, visco-dilation, or iris expansion devices, until the pupil is adequately dilated to proceed with surgery. These patients will still be included in the study, and their pupil size prior to the rescue intervention is still the primary outcome.

- g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely

Participants can choose to stop participating in the study prior to receiving any of the mydriasis agents. Should they choose to withdraw from the study, they would end up receiving routine mydriasis with topical plus intracameral agents. The study ends on post-op month #1 for all individual patients. The study enrollment period will end when the sample size is met.

5. Inclusion/Exclusion Criteria

Inclusion criteria:

Patients aged 40 or older who are undergoing routine cataract surgery under topical anesthesia with monitored anesthesia care at the Wilmer Eye Institute.

Exclusion criteria:

- Need for general anesthesia
- Maximum pupillary dilation <6.0mm at the pre-op clinic visit.
- Prior intra-ocular surgery
- Prior trauma
- Any pre-existing iris abnormalities including pupillary deformity, posterior synechiae, peripheral anterior synechiae, zonular dehiscence
- Pseudoexfoliation
- Allergy to any of the mydriasis agents
- Pregnancy or breastfeeding

6. Drugs/ Substances/ Devices

- a. The rationale for choosing the drug and dose or for choosing the device to be used.

Topical mydriasis will be with 1 drop of phenylephrine 2.5% and 1 drop of cyclopentolate 1% x 4 doses each, with each drop spaced 5 minutes apart given in the pre-op area. These are the standard dilating drops used for cataract surgery. These patients will also receive intracameral lidocaine 1% for anesthesia.

Intracameral mydriasis will be with 0.2ml to 0.3ml of epinephrine 1:10,000 injected into the anterior chamber at the beginning of the cataract surgery procedure. This is the standard concentration use for intracameral mydriasis in cataract surgery. These patients will also receive intracameral lidocaine 1% for anesthesia.

- b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Not applicable. The interventions are all standard FDA approved drugs used for cataract surgery.

- c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Not applicable. The interventions are all standard FDA approved drugs used for cataract surgery.

7. Study Statistics

- a. Primary outcome variable.

Pupil size immediately prior to the capsulorrhexis step of cataract surgery. This will be recorded by digital photography and measured by a researcher who is masked to the intervention.

- b. Secondary outcome variables.

Pupil size immediately after nuclear disassembly, immediately prior to IOL insertion, upon completion of case, and on post-operative day #1.

Need for another mydriatic agent or iris expansion devices during the procedure.

Phaco time and cumulative dispersed energy

Total surgery time

Blood pressure and heart rate in pre-operative area, upon entry into the room, and at the end of the operation.

Other data which will be collected:

DOB

Gender

Race

Iris color

Use of alpha blocker medication

Type and severity of cataract

Complications

- Anterior capsule radialization
- Posterior capsular tear
- Dropped nucleus
- Zonular weakness
- Descemet's tear
- Iris prolapse

Patient Satisfaction Score from 1-10

- c. Statistical plan including sample size justification and interim data analysis.

Based on select prior studies on topical versus intracameral mydriasis, the approximate amount of dilation and approximate size of the dilated pupil can be extrapolated to our study population. Lundqvist et al in 2014 reported that "the pupils dilated with topical mydriatics were 7.45 +/- 1.08 mm at the initiation of the procedure, compared with 7.16 +/- 0.85 mm for the intracameral mydriatics eyes 60 seconds after intracameral mydriatics injection ($p = 0.056$). We would expect the pupil size for pupils dilated with both topic and intracameral mydriatics to be approximately 7.50mm +/- 1.00 mm. The effect size that we are aiming to detect in the size of the dilated pupil is 0.5mm. The alpha is 0.05 and the beta is 0.80.

In a one-way ANOVA study, sample sizes of 70, 70, and 70 are obtained from the 3 groups whose means are to be compared. The total sample of 210 subjects achieves 80% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The size of the variation in the means is represented by their standard deviation which is 0.22. The common standard deviation within a group is assumed to be 1.00.

d. Early stopping rules.

The patient will be removed from the study if they cannot undergo capsulorrhexis and proceed with cataract surgery. Patients with any complications during the surgery will still remain in the study.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Risks of topical mydriasis include: hypertension, tachycardia, ocular discomfort

Risks of intracameral mydriasis include: hypertension, tachycardia, ocular discomfort

Since the current routine protocol for cataract surgery mydriasis involves both topical and intracameral mydriasis, patients participating in this study will not be subject to any increased risk.

b. Steps taken to minimize the risks.

Patients cardiovascular status will be monitored by anesthesia, and anti-hypertensives are given intraoperatively if needed.

c. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems will be reported to Dr Woreta who will report immediately to the IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There are no legal risks in this study. The data will be de-identified at the time of data entry and subjects will be assigned a subject ID number. The log of subject name to ID number will be stored on a password protected computer.

e. Financial risks to the participants.

There are no financial risks to the participants.

9. Benefits

a. Description of the probable benefits for the participant and for society.

The patients in the intracameral alone group may be more comfortable because they will not require any eye drops in the pre-operative area. Due to the fact they are not receiving topical mydriatics, they may have less hypertension and tachycardia as intracameral administration of antibiotics is associated with less systemic absorption.

Current standard of practice is to bring the patients to the preoperative area 90-120 minutes before surgery so they have time to administer topical drops and achieve sufficient dilation. Thus for society, the results of this study have implications for improving the efficiency and reducing time prior to cataract surgery. In addition, it has significant potential to reduce the cost associated with cataract surgery if preoperative drops are eliminated.

10. Payment and Remuneration

- a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

There will be no compensation for participants.

11. Costs

- a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no additional costs beyond the usual standard of care.