Title: No Drop Cataract Surgery: The effect of Intraocular Phenylephrine/Ketorolac Infusion on Retinal Thickness and Macular Edema in Cataract Surgery

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Study Title: No Drop Cataract Surgery: The effect of Intraocular Phenylephrine/Ketorolac Infusion on Retinal Thickness and Macular Edema in Cataract Surgery.

Principle Investigator, Co-investigator(s): Keith Walter MD, Ken Weinlander, MD; Amber Hoang, MD

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Background, Rationale and Context

Patient compliance and insurance coverage with eye drops in cataract surgery has become a major hurdle in successful cataract surgery. One of the major complications of cataract surgery is post-operative pain and cystoid macular edema (CME).[1,2] Multiple topical drugs have been used to prevent pain and macular edema in cataract surgery and include both topical steroid eye drops as well as non-steroidal anti-inflammatory agents (NSAIDs). Issues with these drops include patient difficulty in application, compliance, generic substitution and insurance coverage. A large percentage of patients aren't able to afford these drops or often aren't covered by their insurance. In addition, pharmacists often substitute the intended therapy for a generic version or inadequate drug alternative.[3] Recently, Omidria (phenylephrine and ketorolac injection 1% / 0.3%) was FDA approved for post-operative pain and inflammation in patients undergoing cataract surgery. It is also indicated to maintain pupil dilation during cataract surgery, and is therefore the main reason it is used. Omidria is not a topical drug but a constant infusion of phenylephrine and ketorolac added to the irrigate used during cataract surgery.

Topical NSAIDs have been known to reduce post-operative CME as well as control pain and inflammation, whether alone or with a steroid.[4] Reduction of CME is a major goal of cataract surgery safety. Typically, routine cataract surgery without the protection of a topical NSAID results in 3-4 percent of patient with reduced visual acuity from CME and up to 30% with macular thickening.[4] Prostaglandins formed as a result of the activation of the inflammatory cascade during cataract surgery have been implicated in producing pain, inflammation and macular edema.[5] Prostaglandin formation is drastically reduced by NSAIDs via inhibition of cyclo-oxygenase enzymes (COX 1&2)[6]. In animal studies, sustained suppression of COX enzymes has been shown in all ocular tissues measured up to 12 hours after cataract surgery with the use of Omidria.[7]

All FDA guided studies regarding approval of a topical NSAID, have included a control arm where no anti-inflammatory agents are used. Typically, the control arm subjects require a rescue drug at 2-8%, despite having more anterior chamber inflammation than the study subjects.[8]

We propose to observe whether treating patients with Omidria (phenylephrine and ketorolac injection 1% / 0.3%) during cataract surgery, will not only control post-operative pain and inflammation but also reduce or eliminate cystoid macular edema without adjunctive topical NSAIDs. Potentially all of Dr. Walter's patients undergoing

cataract surgery would be recruited by a study team member, as Omidria is beneficially in maintaining pupil dilation during cataract surgery, and makes the surgery less risky. Only patients which meet an exclusion criterion, such as an allergy to NSAIDs, would not be recruited to participate in the study.

## Objectives

Primary Objective: To determine whether intracameral infusion of Omidria is sufficient alone to prevent post-operative CME and macular thickening.

- *Hypothesis 1*: The administration of Omidria will be sufficient to reduce macular thickening without topical NSAIDs or corticosteroids.
- *Hypothesis 2*: The administration of Omidria will be sufficient to prevent post-operative cystoid macular edema (CME) after routine cataract surgery.

Secondary Objective: To observe whether any patients need additional topical therapy besides the intraoperative medication.

- *Hypothesi*s 1. The administration of Omidria during cataract surgery will preclude any additional need for topical anti-inflammatory drops.

### Methods and Measures

- Design

A prospective interventional study looking at whether Omidria infusion alone during cataract surgery is effective at eliminating post-operative cystoid macular edema and/or macular thickening. We will recruit 200 volunteers undergoing elective routine cataract surgery. Patients may elect to enroll one or both eyes as desired, with both eyes undergoing surgery a week or two apart according to standard cataract surgery protocol. Patients will have no topical anti-inflammatory drops used or provided during the perioperative period. Macular scans via OCT will be taken pre-operatively for baseline measurements, then at about 2 weeks and 6 weeks post-operatively.

We will collect the following demographic data: age, gender, and race. In addition, the presence of macular cysts will be recorded, as well as central macular thickness. Best corrected spectacle acuity will be recorded as well and all data will be stored on a password protected and encrypted computer.

- Setting

The study will be performed at Davie Medical Center at Bermuda Run and will only involve patients undergoing cataract surgery by Dr. Walter.

### Subject selection criteria

Subjects will be recruited through direct asking by a study team member (not Dr. Walter) at the time of cataract diagnosis and selected to participate based on the following inclusion and exclusion criteria.

- Inclusion criteria:
    - Adults age 55-90 years with visual significant cataracts in one or both eyes.
    - Healthy individuals able to tolerate outpatient cataract surgery under local anesthesia via either phacoemulsification and/or femtosecond assisted cataract surgery. Well-controlled diabetes, hypertension will be included.
    - Females of childbearing potential must agree to use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence, oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation or vasectomy of the partner (with confirmed negative sperm counts) in monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or cervical cap or sponge. A pregnancy test is required at least 10 days from the last normal menstrual period, if the patient is a sexually active female of childbearing potential.

- Exclusion criteria:
    - Allergy to Phenylephrine or NSAIDs.
    - Inability to sit steady and upright for the OCT.
    - Complications during surgery, including posterior capsular rupture, vitreous loss, zonular dialysis, or iris trauma.
    - Macular thickness above 300 microns at baseline
    - Currently taking a prostaglandin analogue
    - Presence of an epiretinal membrane on the preoperative OCT.
    - Retained lens fragment post-operatively.
    - Inability to return for follow appointments
    - Female patients who are pregnant, lactating or planning to become pregnant during the course of treatment.

Sample size: 200 patients total.

Study Procedure

- Informed Consent Process: After the patient has been evaluated and meets all of the inclusion and exclusion criteria, a study team member besides Dr. Walter will introduce the study at the time of the subjects' cataract evaluation or at the pre-operative work up. This typically will occur 1 to 8 weeks prior to surgery. The study will be discussed in detail and consent form (appendix 1) will be provided for the patient to review. Written informed consent will be obtained at either at the pre-op holding area or the week prior at the work up for surgery. Written informed consent will only be obtained once the patient has been given time to fully understand the study. If the patient agrees, patients will plan to forsake topical NSAIDs during the perioperative period and will agree to have Omidria

infusion during cataract surgery. As per standard for cataract surgery, patients will return the following day, where the usual measurements will be taken including visual acuity, intraocular pressure, and measurement of anterior cell and flare. The subjects will also return for post op visits at 2 and 6 weeks, where in addition to the above measurements, the macular OCT will be obtained.

- Study Procedure: The enrolled subjects will undergo standard topical phacoemulsification (with or without laser assistance) using Omidria, as labeled by the FDA, throughout the cataract surgery. The Omidria will be provided at no cost to the patient nor the hospital, and will be provided by Omeros. The subjects will be monitored for any usual or atypical outcomes post-operatively. If the patients have atypical eye pain, anterior chamber cell greater than 2+, or macular thickening greater than 50 microns above baseline as documented via the OCT, the patients will be instructed to start a topical NSAID, like bromfenac, and will be used as per standard cataract surgery.

### Outcome Measures

- Best corrected visual acuity at baseline (pre-op), 2 weeks and 6 weeks.
- Presence of Cystoid Macular Edema at 2 weeks and 6 weeks
- Macular thickness at baseline (pre-op), 2 weeks and 6 weeks
- Need for a topical NSAID (rescue med) and reason
- Anterior chamber cell and flare at 1 day, 2 weeks and 6 weeks.

### Analytical Plan

**Results will be analyzed initially using descriptive statistics where applicable. This is not intended to be a comparative study but a utilization, efficacy and safety study. Results will be compared to historical controls with known outcomes in the general population undergoing routine cataract surgery. For example, a recent peer-reviewed paper with a large cohort where bromfenac was used in routine cataract showed an incidence of CME at 3.6%[9]. Dr. Walter, with unpublished data using Omidria on routine cataract surgery, has noted a low incidence of CME at less than 0.5%. We are hoping to show that the use of Omidria is accounting for this reduced rate of CME and macular thickening.**

## Human Subjects Protection

### Subject Recruitment Methods

Subjects will be recruited though direct asking at the time of scheduling their cataract surgery. Patients who decline to participate will be treated exactly the same during and after surgery as those that consent to participate. Participants will be not compensated directly but will likely benefit from not having to pay a co-pay on the normally used topical NSAID. Because of the potential conflict of interest with Omeros, Dr. Walter will not participate in recruiting nor during the consenting process. Dr. Mathew Giegengack will be the medical safety monitor and will review charts and insure no patients were inappropriately recruited or consented.

### Informed Consent

Signed informed consent will be obtained from each subject. The study will be introduced by the study coordinator and informed consent will be obtained formally by a study team member once

the patient fully understands the study. Informed consent will be given 1 or more weeks prior to the patient's surgery, giving them plenty of time to decide and fully understand the study. Final written consent will be obtained by the day the surgery or at the pre-operative work up.

Confidentiality and Privacy

**Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed 3 years after the study is published. They will be destroyed by deleting all files and shredding any documents consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.**

Data and Safety Monitoring

**Dr. Giegengack will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. The study will cease to enroll patients if the CME rate rises above 20%, or if more than half of the patients have atypical pain and/or inflammation requiring a topical NSAID. Greg Russell or a member of his team will help with statistical analysis as we begin data collection.**

Pregnancy in Female Patients

Female patients of childbearing potential will be instructed to notify the investigator immediately (no more than 24 hours after learning of the pregnancy) if pregnancy occurs during the study. If pregnancy occurs, the patient will be withdrawn from the study, and the investigator will discuss the risk of pregnancy and the possible effects to the fetus. Monitoring of the pregnancy will occur until the conclusion of the pregnancy.

Reporting of Unanticipated Problems, Adverse Events, or Deviations

**Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate. Dr. Giegengack has agreed to serve as an unbiased medical monitor.**

References.

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