Protocol: The Impact of Physiologic Cataract Surgery on Patient Comfort and Medication Usage
IIT 98621123 - Matthew Rauen, MD
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NEED *The advanced fluidics of Unity VCS/CS allow a more physiologic cataract surgery environment. Limited research exists comparing the surgical experience for patients between Unity VCS/CS and Centurion with regards to patient comfort and pain.*

STUDY OBJECTIVE *To investigate the impact of Unity VCS/CS with Intelligent Fluidics at a low IOP setting and Centurion with Active Sentry at a traditionally high IOP setting on the intraoperative experience for the patient and surgeon*

STUDY HYPOTHESIS *Unity VCS/CS with Intelligent Fluidics during cataract surgery will result in significantly less discomfort/pain as assessed by the decreased need for rescue medication and lower VAS scores.*

SUPPORTS CLINICAL MESSAGE *Unity VCS/CS allows for phacoemulsification at a more physiologic IOP with lower patient reported discomfort/pain and less pharmacologic use as compared to Centurion with Active Sentry at a traditionally higher intraoperative IOP*

STUDY DESIGN

Cohort	*Bilateral visually significant cataract surgery*	**Endpoints**	***Primary endpoint:*** *% of pts in each group requiring rescue medication for breakthrough discomfort/pain* ***Secondary endpoints:*** • *Discomfort/pain score at phaco, I/A, visco removal* • *Surgeon Experience: Assessment on cooperation & experience* • *Cost-analysis on intraoperative medications utilized in low and high IOP groups* • *Breakthrough pain and discomfort/pain score on subjects with axial length of >24.5mm* • *Post op day 1 patient survey on experience (Iowa Satisfaction with Anesthesia Scale (ISAS)* • *Post op day 1 survey on patient preference - What eye was more comfortable? (R/L)* • *What surgical experience did you enjoy more? (R/L)* • *x% of eyes would undergo the same procedure again* • *x% of eyes would recommend the procedure to family and friends* • *Time Interval between Surgery Completion and Discharge from Facility* • *Physiologic responses by masked anesthesiologist: BP, pulse rate*
Alcon Product	*Unity VCS/CS with Intelligent Fluidics*	**Design**	*Prospective, single-surgeon, eyes undergoing phacoemulsification will be randomized to low (IOP 25mmHg) or high (IOP 65mmHg) IOP, contralateral eye will receive other treatment*
Comparator	*Centurion with Active Sentry (AS)*	**Time of follow-up**	*POD1*

SAMPLE SIZE

85 subjects (170 eyes)

STUDY DURATION (Contract execution to CSR)

13 Months

Introduction:
The study will pertain to investigating the impact of high vs low IOP on the intraoperative experience and comfort for the patient and surgeon. Our hypothesis is that operating at a more physiological IOP using Unity VCS/CS and Centurion with Active Sentry at a higher, or more traditional IOP will result in significantly less discomfort/pain as assessed by the decreased need for rescue medication and lower VAS scores.

Background:
Although topical anesthesia provides for high patient comfort during cataract surgery, certain parts of the cataract procedure are associated with more patient discomfort. To further increase patient comfort while undergoing cataract surgery under topical anesthesia, it was proposed to add intracameral lidocaine.[1] Injection of intraocular lidocaine increases patient cooperation and decreases the degree to which patients are bothered by tissue manipulation, two outcomes that justify its use.[2]

It is plausible that the use of intracameral lidocaine became 'routine care' in an era where surgeons strived for more efficient cataract surgery through altering fluidics by increasing vacuum level, flow rate, and infusion pressure. The desire for increased efficiency also led to the addition of a variety of other pharmacological agents, such as sympathomimetic agents, other analgesics, NSAIDs, opioids, etc.[3]

Despite technological and procedural advances in ophthalmic surgery, the prescription rate for opioids after ophthalmic procedures, including cataract surgery, has been paradoxically increasing[4]

In Scarfone et al., the patient's subjective perception of pain was significantly lower for the low intraoperative pressure group (IOP 30 mmHg) as compared to high IOP group (80 mmHg) according to the Wong Baker faces scale[5]

In Rauen et al., lower intraoperative pressures at the time of cataract surgery were associated with less pain by real-time VAS scoring and less medication usage.[6]

The PI has completed thousands of cataract surgeries with physiologic (low) IOP (intraocular pressure) and standard (high) IOP (intraocular pressure). A previous study completed at our facility showed equivalent visual outcomes between the two conditions at day 1, 7, 30, and 90. Additionally, case time did not differ between the two conditions. A preliminary study completed by the PI suggested physiologic (low) IOP surgery was more comfortable by Visual Analogue Scale (VAS). Furthermore, in this same pilot study, physiologic (low) IOP surgery led to less narcotic and less anxiolytic medication use. While we recognize that high IOP surgery is standard of care, more physiologic (low) IOP surgery again has been proven safe and may be more comfortable.

Objective/ Unmet Medical Need:
To investigate the impact of Unity VCS/CS with Intelligent Fluidics at a low IOP setting and Centurion with Active Sentry at a traditionally high IOP setting on the intraoperative experience for the patient and surgeon. Limited research on phacoemulsification at near physiological IOP and its impact on patient discomfort/pain using the Unity VCS/CS system.

Design:
Prospective, single-surgeon, eyes undergoing phacoemulsification will be randomized to high (IOP 65mmHg) or low (IOP 25mmHg) IOP, contralateral eye will receive other treatment.

Study treatment & Methods:

- Sequential cataract surgery with similar cataract grade 2-3+ based on LOCS III grading bilaterally; 2nd eye to be completed within 2-3 weeks of first eye
- Randomize first eye to low vs high IOP, contralateral eye receives opposite IOP
- Patient education on VAS with standard script
- Standard pre-op drops: 2 drops of cyclopentolate 1%, tropicamide 1%, flurbiprofen sodium (Ocufen 0.03%), phenylephrine hydrochloride 2.5%, and 3 drops of marcaine 0.05%
- After draping, patients receive OcuCoat on cornea and 3 drops of lidocaine, 1mg of Versed (midazolam for anxiety with no analgesic effects)
- If patients experienced breakthrough pain during surgery, additional topical anesthetic, intracameral lidocaine, and/or opioid will be used per surgeon discretion and stage recorded
- Physiological responses recorded: Anesthesiologist will monitor patients per standard of care but will record additional BP/HR values at the start of the case (room entry), 4 minutes after versed is administered, during phacoemulsification, and during viscoelastic removal.
- Technique and Intraoperative recordings:
    - Single surgeon, uniform corneal incision construction (size, architecture) and use of Intrepid coaxial polymer I/A curved, Alcon OVD-Duovisc; Horizontal phaco-chop technique with preestablished, standardized, and optimized fluidic parameters
    - VAS score is asked at beginning of: phaco, cortex infusion /aspiration, viscoelastic removal
    - Surgeon assessment on patient cooperation and overall experience
    - Recording of intraoperative phacoemulsification metrics to ensure comparable parameters to eliminate variables other than IOP that may contribute to physiological changes
    - CDE, ASM activation, total aspiration time

Key Assessments:
Percent of patients in each group requiring treatment for breakthrough discomfort/pain
Discomfort/pain score at phaco, I/A, visco removal (Real time VAS scoring)

- VAS score : 0 – no pain, 10 – unbearable pain
- VAS scored after each stage with false positive and false negative controls that are utilized to disqualify subjects out of study
- False positive: visco injection/capsulorhexis - should not experience pain
- False negative: drape removal – should experience pain/pressure (alert enough to participate)

Physiologic Responses associated with pain/inflammation: Blood pressure, Pulse rate
Surgeon Experience: Assessment on patient cooperation & surgeon intraoperative experience. Surgeon assessment on patient cooperation: poor, good, excellent:

- 1- Poor cooperation: could not follow instructions, lid squeezing, patient had frequent eye & head movements
- 2- Good cooperation: able to follow directions 50% of the time, some lid squeezing and patient movement 3- Excellent cooperation: able to follow directions >80% of the time with limited lid squeezing and patient movement

Surgeon assessment on overall experience: poor, good, excellent

    - 1- Poor: fluctuating chamber (reverse pupillary block or surge) and reduced efficiency (nucleus & cortex removal)
    - 2- Good: >75% chamber stability and adequate efficiency
    - 3- Excellent: Minimal to no fluctuating chamber and excellent efficiency

Cost-analysis on intraoperative pharmacological agents utilized between high vs low IOP
Sub-analysis on subjects with axial length >24.5mm
Time Interval between Surgery Completion and Discharge from Facility to evaluate post-op efficiency and recovery time of patients

- Follow up- Patient Surveys:
    - Post op day 1 patient survey on experience (Iowa Satisfaction with Anesthesia Scale (ISAS)
    - Post op day 1 survey on patient preference - What eye was more comfortable? (R/L)What surgical experience did you enjoy more? (R/L)
    - x% of eyes would undergo the same procedure again
    - x% of eyes would recommend the procedure to family and friends

Primary Endpoint:

% of pts in each group requiring rescue medication for breakthrough discomfort/pain

Secondary endpoints:

- Discomfort/pain score at phaco, I/A, visco removal
- Surgeon Experience: Assessment on cooperation & experience
- Cost-analysis on intraoperative medications utilized in high vs low IOP groups
- Breakthrough pain and discomfort/pain score on subjects with axial length of >24.5mm
- Post op day 1 patient survey on experience (Iowa Satisfaction with Anesthesia Scale (ISAS)
- Post op day 1 survey on patient preference - What eye was more comfortable? (R/L)
- What surgical experience did you enjoy more? (R/L)
- x% of eyes would undergo the same procedure again
- x% of eyes would recommend the procedure to family and friends
- Physiologic responses by masked anesthesiologist: BP, pulse rate
- Time Interval between Surgery Completion and Discharge from Facility

Study Procedures:

Duration of study will be approximately 13 months. At the time of their initial evaluation, consent process will include regular discussion and informed consent for cataract surgery. Risks, benefits, and alternatives to cataract surgery will be discussed. Patients who meet inclusion criteria will be offered additional discussion regarding the study. This discussion will include the elective nature of the study and detailed discussion of the informed consent document provided by surgeon (with study coordinators readily available). In addition, a copy of the informed consent document will be provided to the patient for their review.

Study Rationale:

The study will involve MAC (Monitored Anesthesia Care) for all patients; this is used for all cataract surgeries in our center. This style of anesthesia includes baseline topical anesthetic drops (Marcaine) placed in pre-op, anesthesiologist administering baseline anxiolytic medication (Midazolam) in the operating room, and just prior to initiating surgery surgeon administers lidocaine. With all cases in our facility, both the surgeon and anesthesiologist monitor for comfort, cooperation, and need for

additional anxiolytic or analgesia. The goal of MAC anesthesia is to provide comfort. While we strive for a pleasant experience for our patients, this is not general anesthesia, and there is a desire for patients to have the ability to follow commands. While some patients have some element of amnesia with this form of anesthesia, not all do. Participation in the study will not prevent surgeon or anesthesia professionals from adding additional anesthesia throughout the case if required for comfort or cooperation.

Subject Selection:
Subjects who will require bilateral cataract surgery will be considered. Evaluations will occur in the clinic of the Principal Investigator (PI) Matthew Rauen, MD at the Wolfe Eye Clinic.
Inclusion Criteria:

- Visually significant cataract 2-3+ undergoing uncomplicated cataract surgery with similar cataract grade in both eyes
- Unremarkable ocular health but inclusive of early AMD

Exclusion Criteria:

- H/o ocular surgery including corneal refractive surgery
- Compromised zonular integrity or stability
- Uncontrolled diabetes and diabetic retinopathy
- Small pupils
- H/o systemic inflammatory disease/uveitis
- H/o chronic pain medications (including narcotics) and benzodiazepine usage
- Abnormal liver or renal function

Study Cost/Reimbursement:

- Participation in this study will be of no additional cost to patients. Insurance will partake in the payment of study evaluation and standard cataract surgery. The additional data monitoring needed will be provided at no cost to patients and incurred by the Sponsor.
- At the completion of the study patients who have completed the study in its entirety will be mailed a check for $150.00.

Planned Data Analysis:
The following analysis will be performed using STATA software (v16.1, College Station, TX). All continuous variables will be summarized using mean, standard deviation and standard error. All binary measures will be summarized as proportions with standard deviation. The results of the test for normality on each continuous measure (the Shapiro-Wilk test) will determine whether the paired t-test or the Wilcoxan Sign Rank test will be used. McNemar's test will be used to compare proportions in binary outcome data, and the chi-squared test will be used to analyze the categorical outcome.
The analysis will follow a hierarchical approach using the following order of testing, only proceeding to the next test if the prior test achieves statistical significance at a level of 0.05.
Primary endpoint: comparing low vs. high IOP groups

1. Proportion of patients requiring rescue medication for breakthrough pain

Secondary Endpoints: comparing low vs. high IOP groups

1. Discomfort/pain score (VAS) - CONTINUOUS
    a. Phacoemulsification
    b. I/A
    c. Visco removal

2. Surgeon Experience - CONTINUOUS
    a. Patient cooperation
    b. Surgeon experience
3. Cost analysis of intraoperative medications used - CONTINUOUS
4. Discomfort/pain score (VAS) on subjects with axial length of >24.5mm - CONTINUOUS
    a. Phacoemulsification
    b. I/A
    c. Visco removal
5. Post op day 1 patient survey on experience (Iowa Satisfaction with Anesthesia Scale (ISAS) - CONTINUOUS
6. Proportion of patients following each procedure who would undergo the same procedure again - BINARY
7. Proportion of patients following each procedure who would recommend the procedure to family and friends - BINARY
8. Time Interval between Surgery Completion and Discharge from Facility - CONTINUOUS
9. Post op day 1 survey on patient preference - Which eye was more comfortable? (R/L/Neither) - CATEGORICAL
10. Which surgical experience did you enjoy more? (R/L/Neither) – CATEGORICAL
11. Proportion of patients who experience a significant (as defined by Crandall[1]) physiologic response by a masked anesthesiologist - BINARY
    a. Change in diastolic BP from baseline
    b. Change in systolic BP from baseline
    c. Change in pulse rate from baseline

Sample Size Justification

Assuming a power of 80%, a significance level of 0.05, and a two-tailed testing strategy, and assuming 15% of patients in the high IOP group compared with 0% of patients in the low IOP group will require break-through medication (Rauen, prepublication), a sample size of 58 pairs and 116 eyes is needed to detect a difference. Accounting for 15% attrition, a sample size of 67 patients is recommended. If the site accounts for that correlation in the sample size calculation, the recommended sample size is 85 patients, 170 eyes.

Data Collection and Management:

Study worksheets will be created before data collection. At the conclusion of each week, all completed patients will have data collected transferred to a password protected excel spreadsheet. There will be no names placed into this document – only medical record numbers will be used for identification. To facilitate data entry, the worksheets coincide with excel. The design of the data entry screens will follow the same flow as the provided worksheets to ensure minimal issues during data entry. All worksheets collected for study (anesthesia and surgeon) will be placed into study binders. Study binders will be placed inside of locked cabinet.

Any corrections to the worksheets will be made by drawing a single line through the incorrect entry, recording the correct information, and initialing and dating the change. The study worksheets and data entered in the Excel files will be audited by the study sponsor.

Data is protected by preventing unauthorized users from accessing the system with the use of username and password combination. In addition, each individual user will be assigned a specific role in the Microsoft Excel which will grant that user the right to view, edit and/or delete the data.

All clinical data generated in the study will be submitted to the Sponsor or its designee for quality assurance review and statistical analysis. All worksheets and data entered in Excel files will be reviewed for completeness and evident recording errors will be rectified by contact with the appropriate clinical site.

Study Administrations:
Ethical and Regulatory Considerations- the study is conducted in accordance with the following:
• Protocol and study-related plans and documents
• Local regulations, as applicable
• Good Clinical Practices, as outlined in the ICH Harmonized Tripartite Guideline for GCP (ICH E6(R2))
• The ethical principles established by the Declaration of Helsinki
• Regional participant data protection laws and regulations

Institutional Review Board (IRB):
The study site must maintain an accurate and complete record of all reports, documents and other submissions made to the Institutional Review Board (IRB) concerning this protocol.
The investigator must supply ongoing study progress reports to the IRB, per local requirements, such as updates on SAEs, protocol deviations and amendments, ICF revisions, relevant sponsor communication, enrollment updates, etc. In addition, the investigator must notify the IRB at the closure of the study.

Informed Consent:
It is the responsibility of the investigator or his/her designee to inform each subject of the purpose of this study, including possible risks and benefits and document the informed consent process in the subject's chart. Prior to entry into the study or initiation of any study-related testing, the subject must read, sign and date the informed consent form. If the subject's vision is impaired to the point where they cannot read the informed consent document, the document will be read to the subject. The person executing the consent must also sign and date the consent form. One original informed consent form is to be retained by the study site, and a copy is to be given to the subject.

Protocol Amendments:
This protocol must be followed as written. Any change or addition to this protocol that impacts subject safety, or the validity of the study requires a written protocol amendment that must be approved in writing by the IRB and any required regulatory authorities before implementation.

Record Keeping and Retention:
Data generated for the study should be stored in a limited-access file area and be accessible only to representatives of the study site. All reports and communications relating to study participants will identify participants only by subject identification number. Complete subject identification will be kept by the investigator. This information will be treated with strict adherence to professional standards of confidentiality.

- Documents Provided to Sponsor: A copy of the IRB approved informed consent form.
- Documents that study site will retain:
    - All original informed consent forms with required signatures.
    - All participant source documents, etc.
    - All IRB correspondence (i.e., informed consent [including any approved revisions], protocol, AE, advertisements, newsletters).

- Copies of all pertinent correspondence pertaining to the study (except budget issues) between the Sponsor or its designee and the site

Confidentiality:
All clinical study findings and documents are regarded as confidential. Study documents (protocols and other material) must be stored appropriately to ensure their confidentiality. The investigator, site personnel, and members of the IRB must not disclose such information without prior written approval from the Sponsor. The anonymity of participants must be maintained per applicable local and national laws. Subjects are specified on all documents by subject number but not by name. Documents that identify the subject, e.g., the signed ICF, must be maintained in confidence by the investigator. Site personnel must obliterate participant names from study-required documents that identify the subject by name, e.g., hospital records, prior to transmitting these documents to Sponsor or its designee.

Publication:
Data and information generated in this study are the exclusive property of the Sponsor and are confidential. At the end of the study, a clinical study report will be written by the Sponsor or its designee. Written approval from the Sponsor is required before disclosing any information relative to this clinical study, and no publications initiated by investigators may be published until all protocol-defined results are published in a manuscript. Publication of the results must be based on appropriate analyses and review of the complete data. Authorship may be determined based on enrollment of eligible subjects or contribution to the design, conduct, or interpretation of the study. Investigators agree to have their names listed as an investigator in any publication reporting the results from this study, whether they are an author on the publication. The preparation and submittal for publication of manuscripts and presentations containing the study results shall be in accordance with a process determined by mutual written agreement between the Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws.

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