Microscope-Integrated Optical Coherence Tomography Can Measure the Volume of Subretinal Blebs Created by a Suprachoroidal Approach

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OBJECTIVE The authors seek to study the feasibility of creating subretinal blebs via a novel suprachoroidal technique while utilizing intraoperative OCT imaging to measure the volume of subretinal blebs.

PURPOSE This study aims to advance recent work on the use of imaging modalities to measure the volume of medication delivered into the subretinal space. It specifically examines the volume of subretinal blebs created by a novel subretinal drug delivery device utilizing microscope-integrated optical coherence tomography (MIOCT).

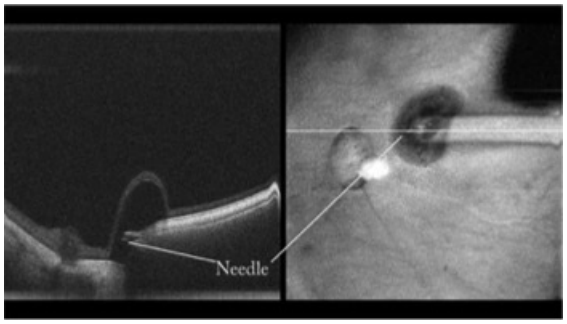
METHODS An MIOCT image-based volume measurement method was developed and assessed for accuracy and reproducibility by imaging ceramic spheres of known size that were surgically implanted into ex-vivo porcine eyes. The images were manually segmented, and the segmented images were used to develop a voxel-to-volume conversion formula. This method was then used to measure subretinal blebs created in 10 porcine eyes by injection of balanced salt solution utilizing a novel suprachoroidal cannula (Orbit Biomedical). Bleb volumes obtained from MIOCT were compared to the intended injection

volume. The manually segmented blebs were also used to develop an auto-segmentation deep learning algorithm.

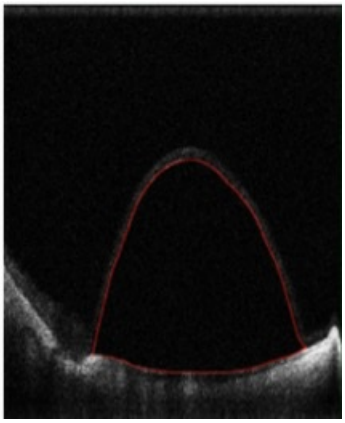
RESULTS The mean calculated volume of the ceramic spheres was 0.847 +/- 0.041 mm3. Comparison to the actual volume of 0.524 mm3resulted in a calibration factor 0.619 (σ = 4.8%). A Monte Carlo simulation found a +/- 4.8% segmentation uncertainty error. The total uncertainty = √calibration uncertainty2+ segmentation uncertainty2= √4.82+ 4.82= 6.8%. The mean control volume injected by suprachoroidal device was 66.44 µL (σ = 2.4 µL). The mean entry bleb volume was 5.14 µLwith a standard deviation of 1.68µL. The mean subretinal bleb volume (total bleb volume minus entry bleb volume) was 54.8 mm3(σ = 12.3 mm3). The minimum, median, and maximum subretinal bleb volume was 32.8 µL, 57.45 µL, and 69.6 µL, respectively.The mean subretinal bleb volume was 82% of the intended injection volume and the mean percent error of the mean measured volume relative to the mean intended volume was 18%.

CONCLUSION MIOCT can measure the volume of subretinal blebs with accuracy and precision. It provides a method for visualization and quantification of subretinal drug delivery and enables surgeons to evaluate the success of subretinal drug delivery. The novel, suprachoroidal delivery approach using the Orbit Subretinal Delivery System was effective and accurate in volume delivery as assessed by MIOCT.

HUMAN RESEARCH No: Study does not involve human research



Entry bleb captured intraoperatively by MIOCT with the B-scan (left panel) and en-face (right panel) view created by a novel, suprachoroidal delivery approach using the Orbit Subretinal Delivery System.



Intraoperative OCT image of a full subretinal bleb created by a suprachoroidal delivery system with manual segmentation. (Red- Traced boundary)

Particulate Matter From Syringes Used for Intravitreal Injections

- Roger A. Goldberg, MD, MBA
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- Olga Laskina

OBJECTIVE To quantify how much particulate matter is present both in transfer (short term; i.e., minutes from glass vial to vitreous cavity) or storage (longer-term; i.e., days to weeks) syringes.

PURPOSE Recent FDA guidance is driving increased scrutiny over visible and sub-visible particulates in intravitreal injections. This has led to a shift away from silicone-lined syringes, though little data exist on the particulate counts in other syringe systems. This study aims to quantify particulate matter across four syringe types, when used either for short term transfer, or for longer-term storage.

METHODS Four syringe systems were studied: a siliconized polypropylene insulin syringe, a silicone-free polypropylene syringe lubricated with oleamide, a glass prefilled syringe lubricated with baked-on silicone oil, and a silicone-free / lubricant-free cyclic olefin polymer (COP) prefilled syringe. Syringes were either rinsed with water or stored for up to 90 days filled with phosphate buffer; particle levels in the fluids were then quantified by Flow Imaging. Particle formation after 24 hours of agitation of a bevacizumab formulation was also characterized in the two prefilled syringe systems.

RESULTS Insulin syringes showed very high particle counts – nearly two orders of magnitude higher than USP <789> limits with water rinsing alone. Silicone-free polypropylene syringes lubricated with oleamide had substantially lower particle levels as compared to insulin syringes but showed an appreciable increase in particles over time (leading to visible particle formation), possibly due to the migration of the lubricant into solution. Baked-on silicone glass prefilled syringes and silicone-free / lubricant-free COP prefilled syringes both showed low particle levels in the greater than 10 micron size range. However, the COP syringes showed the lowest overall particle levels in the greater than 1 micron size range and the lowest particle levels with bevacizumab agitation.

CONCLUSION Different syringe systems have different intrinsic particle loads which can contribute directly or indirectly (by facilitation of protein aggregation) to particle loads in the delivered drug product. Silicone-free transfer syringes lubricated with oleamide appear to have time-dependent particle loads and are associated with the formation of visible particles after 30 and 60 days of storage.

HUMAN RESEARCH No: Study does not involve human research

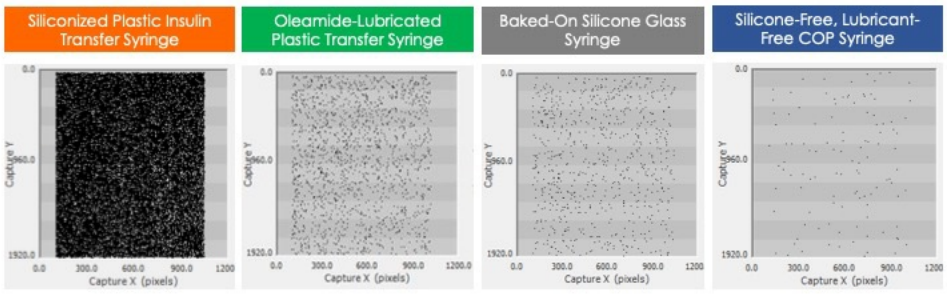


Figure: Flow imaging particle counts (all particles > 1 µm) as x-y spatial plots on the instrument detector. Syringes were filled with approximately 0.5 mL of buffer (no drug product), subjected to ASTM D4169-14 drop / shipping testing, and stored for 15 days at 2-8°C.

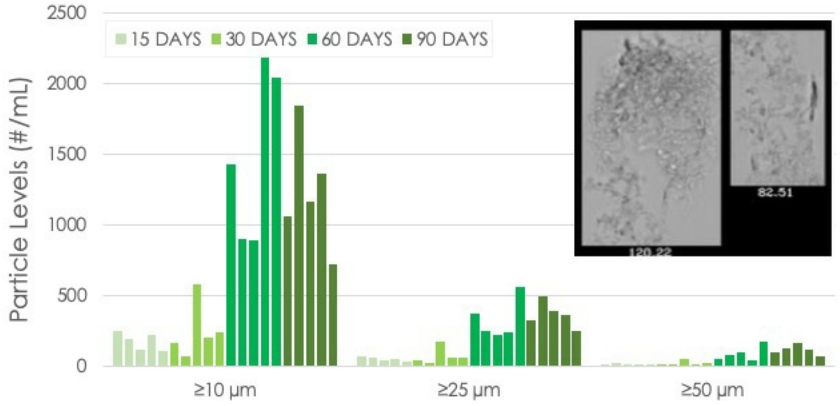


Figure: Time evolution of particle counts in NormJect silicone-free, lubricated plastic transfer syringes filled with buffer (no drug product). Each bar represents one single syringe and 5 syringes were measured at each time point: 15, 30, 60, and 90 days storage. The inset image shows characteristic particles detected by FlowCam in the NormJect syringes at 90 days.

Post Hoc Analysis of Suprachoroidal Injection Experience Across Retinal Disease Indications

- Christopher R Henry, MD
- Cherry Wan, MS
- Barry Kapik, MS

OBJECTIVE To assess injection experience and consistency of suprachoroidal (SC) injections of an investigational formulation of triamcinolone acetonide (CLS-TA) across retinal disease indications.

PURPOSE SC injections have been performed over 1,000 times and have emerged as an effective drug delivery route to the posterior segment. Post hoc correlations were performed between procedural and patient characteristics across 3 retinal disease indications and 6 prospective clinical trials. Injection completion rate with 900 µm needle, as opposed to switching to an 1100 µm needle, was evaluated.

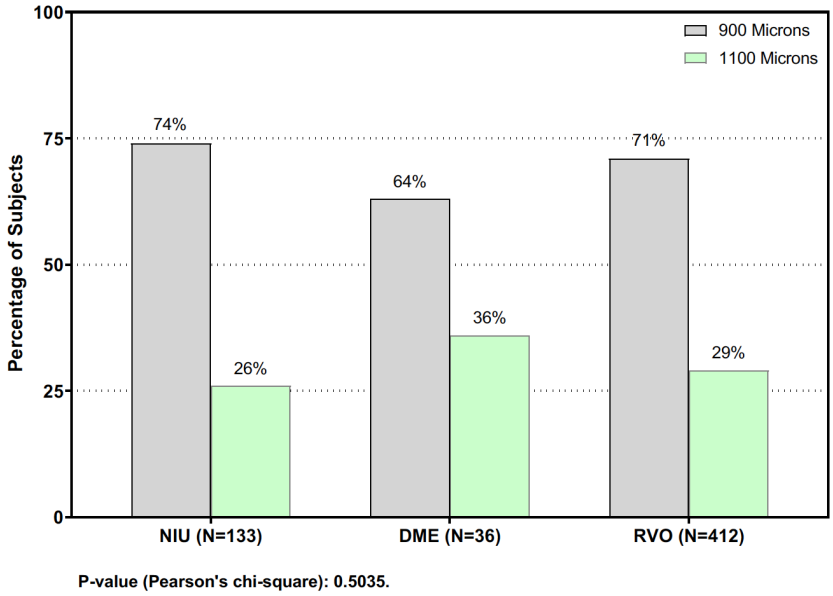
METHODS Post hoc analyses were conducted to evaluate the relationship between needle length for baseline SC injection and patient characteristics across 6 prospective clinical trials (AZALEA, PEACHTREE, TYBEE, TANZANITE, SAPPHIRE and TOPAZ) and 3 retinal diseases (non-infectious uveitis with macular edema, diabetic macular edema and retinal vein occlusion). Pearson chi-square analysis and biserial correlations were performed for univariate analysis of categorial and continuous variables, respectively. Multivariate logistical regression was developed to confirm univariate findings.

RESULTS Overall, 99.8% (581 of 582) of baseline suprachoroidal injections were successfully completed. Among the successful injections, 71% (412 of 581) were completed with the 900 µm needle while 29% (169 of 581) were completed with an 1100 µm needle. In both univariate and multivariate analyses, no statistical relationships were found between needle length and retinal disease indication, age, visual acuity, intraocular pressure, central subfield thickness, lens status or race. Gender and administration quadrant were found to statistically ($p<0.05$) correlate with needle length both in the univariate and

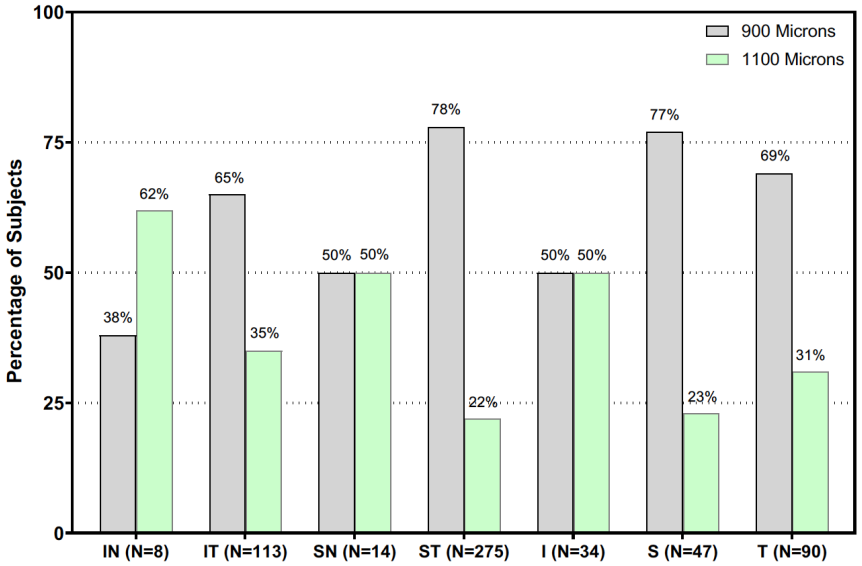
multivariate analyses: 76% (209 of 275) of injections were completed with 900 µm needles for female patients while 66% (202 of 306) were completed for male patients. Additionally, 78% (214 of 275) of injections were completed with the 900 µm needle in the superotemporal quadrant while 65% (73 of 113) were completed in the inferotemporal quadrant, which is consistent with literature reports of thinner sclera in the superior hemisphere at the level of the pars plana.

CONCLUSION To date, this is the largest aggregate dataset of SC clinical injections with mounting evidence pointing to the reliability and consistency of the procedure. The two needle length options successfully accommodate for anatomical variations across patients and retinal disease states. This data supports the superotemporal quadrant as a preferred location for performing SC injections.

HUMAN RESEARCH Yes: Approved by institutional review board



No statistical correlation was found between microneedle length (900 vs 1100 micron) and retinal disease indication.



P-value (Pearson's chi-square): 0.0005.

A statistically significant correlation was found between administration quadrant (superotemporal) and microneedle length.

Results From the Phase 3 PEACHTREE Clinical Trial: Systemic Therapy and the Efficacy of CLS-TA, a Post Hoc Analysis

- Ashvini K. Reddy, MD
- Thomas A. Ciulla, MD, MBA

OBJECTIVE The objective of this post hoc analysis is to explore the effect of systemic corticosteroid and steroid-sparing therapies on the efficacy of CLS-TA in patients in the Phase 3 PEACHTREE trial.

PURPOSE Treatment of uveitis may require a combination of systemic and local therapies. This analysis explores the efficacy of suprachoroidal (SC) CLS-TA, a proprietary suspension of triamcinolone acetonide, in the PEACHTREE trial for noninfectious uveitis, to patients receiving and not receiving other systemic therapies.

METHODS In PEACHTREE, 160 patients were randomized 3:2 to receive SC CLS-TA or sham at baseline and week 12. Patients were allowed to be included in PEACHTREE if on a low dose corticosteroid or stable dose of immunomodulatory therapy. The primary endpoint was the percentage of patients with an increase of ≥ 15 letters in EDTRS best corrected visual acuity (BCVA). Secondary endpoints included mean change from baseline in BCVA and central subfield macular thickness (CST). Post-hoc analyses were performed to evaluate the improvement in BCVA and CST in patients receiving systemic corticosteroid and/or steroid-sparing therapy at baseline, and in patients receiving no systemic therapies.

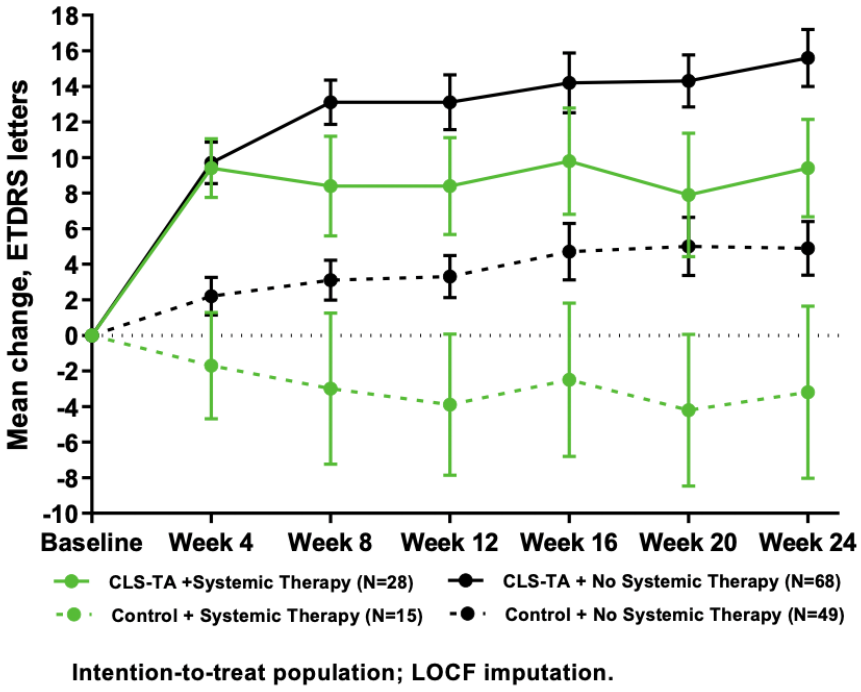
RESULTS Overall, 46.9% of patients in the active arm gained ≥ 15 letters at week 24 versus 15.6% in the control. The mean change from baseline BCVA was 13.8 letters, versus 3.0 in the control. The mean CST reduction was 152.6 µm in the active arm vs. 17.9 µm in the control. For the post-hoc analyses, 68 patients in the active arm and 49 in the control received no additional systemic therapies (systemic corticosteroid or steroid-sparing). At

week 24, the increase in BCVA was 15.6 letters versus 4.9 letters in the control arm ($p < 0.001$) and reduction in CST was 169.8 µm versus 10.3 µm in the control ($p < 0.001$). Further, 28 patients in the active arm and 15 in the control were receiving systemic corticosteroid and/or steroid-sparing therapy at baseline. At week 24, the change in BCVA was +9.4 letters in the active arm versus -3.2 letters in the control arm ($p = 0.002$) and reduction in CST in the active arm was 108.3 µm versus 43.5 µm in the control ($p < 0.001$).

CONCLUSION These post hoc results corroborate the prespecified study analyses in the PEACHTREE trial. With respect to BCVA and CST, a clinically meaningful relative benefit of CLS-TA over control was noted, with and without systemic corticosteroid or steroid-sparing therapy.

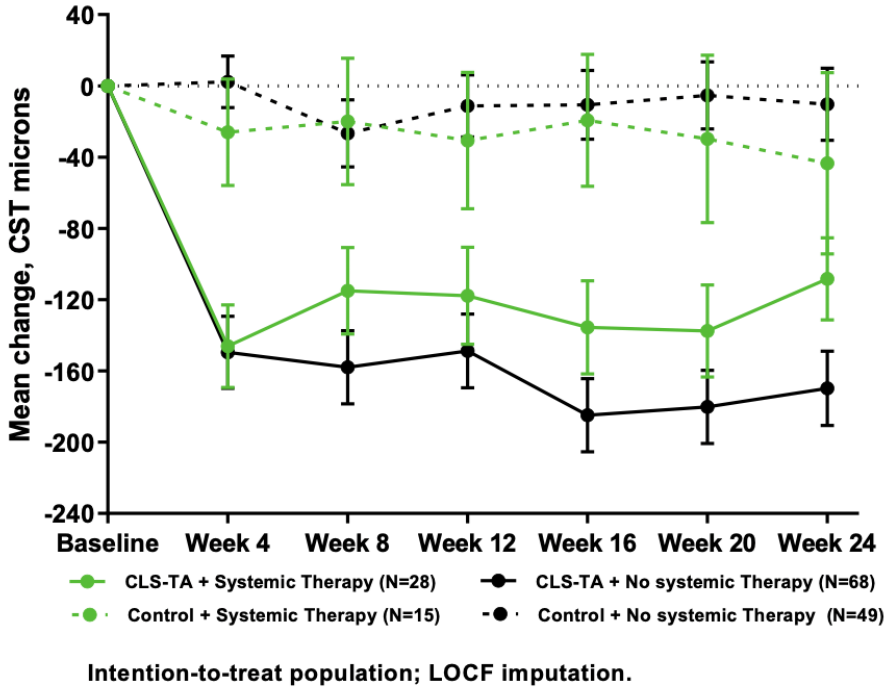
HUMAN RESEARCH Yes: Approved by institutional review board

FIGURE 1. Mean Change from Baseline in BCVA by Use of Systemic Corticosteroid/ Steroid-Sparing Therapy



Change in visual acuity from baseline comparing patients recieving CLS-TA with and without systemic immunosuppression compared to controls with and without immunosuppression.

FIGURE 2. Mean Change from Baseline in CST by Use of Systemic Corticosteroid/Corticosteroid-Sparing Therapy



Intention-to-treat population; LOCF imputation.

Patients receiving CLS-TA treatment had greater reduction in central subfield thickness (CST) than controls. Patients able to discontinue or avoid systemic immunosuppression with CLS-TA had lower CST than CLS-TA patients receiving immunosuppression.

Cooling Anesthesia for Intravitreal Injection With a Novel Device: Results of the Prospective COOL-2 Study

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- Arshad M. Khanani, MD
- Charles C. Wykoff, MD, PhD
- Gun-Ho Kim, PhD

OBJECTIVE To evaluate the safety & efficacy of a novel cooling device capable of achieving ocular surface anesthesia within 10 seconds prior to intravitreal injection (IVT).

PURPOSE Anesthesia for IVT can cause discomfort for patients and is a known bottleneck for clinical efficiency. Novel approaches that can improve patient experiences and optimize workflow efficiency are needed.

METHODS Results from an ongoing, multicenter, open-label study evaluating repeated cooling anesthesia administrations will be presented (COOL-2; NCT03956797). Key inclusion criteria were patients receiving IVT injections who had received at least 3 prior IVT. Key exclusion criteria were a history of ocular inflammation or previous retinal surgery. Cooling anesthesia was applied in lieu of their regular anesthesia, and pain was recorded as part a visual analog scale at time of injection. Comprehensive anterior and posterior segment exam was performed 30 minutes post injection. Adverse events and time to perform IVT were recorded. Patient reported preference for anesthesia type was captured.

RESULTS 52 patients have been enrolled with a mean of 3.1 cooling applications per patient (166 cooling applications total) thus far. There have been no serious adverse events. Nonserious AEs include 19% incidence of subconjunctival hemorrhage related to IVT, not to cooling administration. Pain during IVT, as measured by visual analog scale, was not significantly different compared to historical controls and similar to standard of care anesthesia. 70% of subjects reported preference for cooling anesthesia compared to their prior anesthesia method (subconjunctival lidocaine). Total anesthesia+IVT time with cooling was less than 2 minutes, significantly shorter than that required for subconjunctival lidocaine.

CONCLUSION Cooling anesthesia for IVT can be a safe and effective anesthetic method

which may improve the intravitreal injection experience for patients as well as improve workflow efficiency for clinicians.

HUMAN RESEARCH Yes: Approved by institutional review board

Lens and Peripheral Retinal Relationships During Vitrectomy: Comparison of 23, 25, and 27-Gauge Vitrectomy and Curved Endolaser Probes

- Jayanth Sridhar, MD
- William E. Smiddy, MD
- Sander R Dubovy, MD
- Jacob Starr Duker, MD
- Michael J Venincasa, BS

OBJECTIVE There are no available pathologic data on the relationships between smaller-gauge vitrectomyinstruments inserted in the eye and the crystalline lens and whether there are differences basedon gauge. This study seeks to describe those relationships.

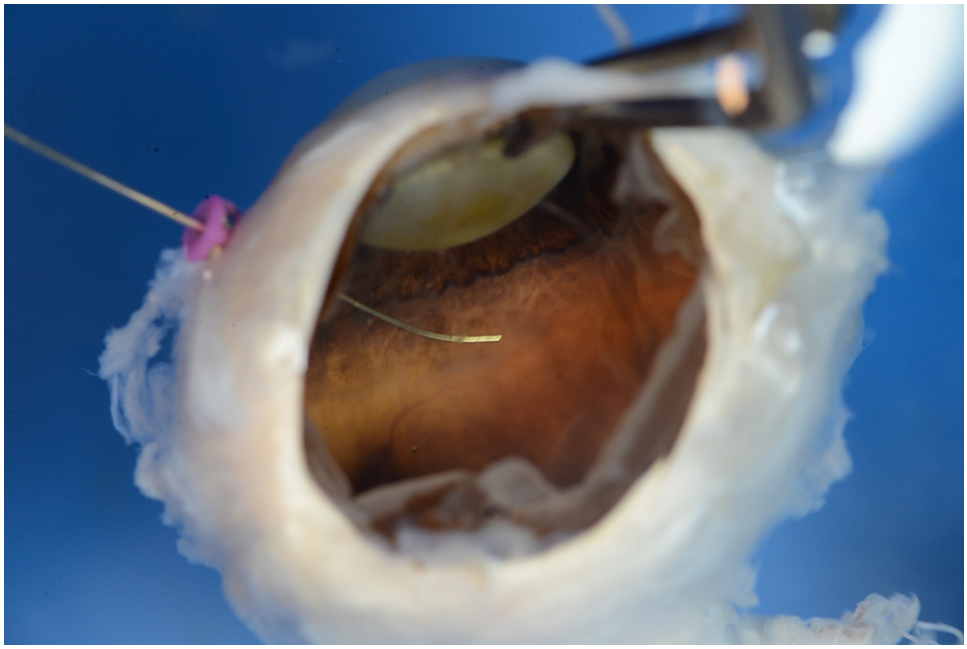
PURPOSE To compare relationships between the crystalline lens and vitrectomy instruments ofdifferent gauges.

METHODS Eight fresh phakic cadaver eyes were utilized after fixation. For each eye a 27-gauge,25-gauge, and 23-gauge valved trochar were sequentially placed in the superotemporal quadrant4mm posterior to the limbus. For each gauge, measurements of intraocular relationships weretaken using vitrectomy and curved endolaser probes. Statistical analyses were conducted usingthe Kruskal-Wallis and Wilcoxon tests.

RESULTS There were no significant differences in maneuverability relative to the lens betweeninstruments of different gauge size. The average distance from instrument to lens at thegeometric center of the globe was 5.5 mm. In all eyes, vitrectomy and endolaser probes of anygauge could access the peripheral retina on both sides of the sclerotomy in the adjacent 3-4 clockhours to the sclerotomy without touching the lens. The instruments could be advanced withoutlens touch to contact the retina at least within 23 mm of the ora serrata 180 degrees away fromthe insertion site.

CONCLUSION Vitrectomy and curved endolaser probes achieved similar maneuverability relativeto the lens regardless of gauge. This study confirms that small-gauge vitrectomy instrumentshave considerable access to the peripheral retina in phakic eyes.

HUMAN RESEARCH No: Study does not involve human research



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The Effect of Latency on Digital Vitreoretinal Surgery

- David Tri Ta Kim, MD FRCSC
- David R. Chow, MD, FRCS(C)

OBJECTIVE What is the effect of latency on surgical performance using a three-dimensional heads-up display (3D HUD) visualization system for vitreoretinal surgery.

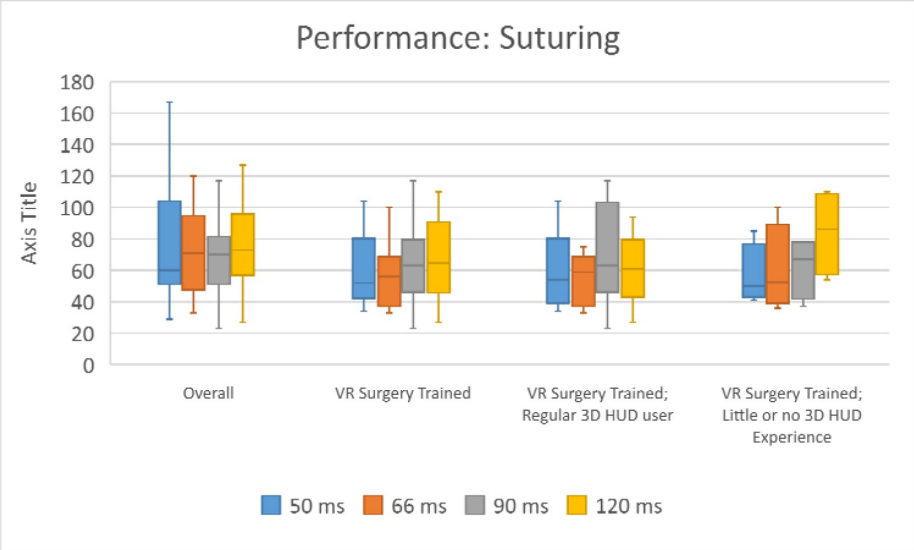
PURPOSE Different three-dimensional heads-up display visualization systems for vitreoretinal surgery have started to be used recently. Latency is one proposed disadvantage over the traditional optical microscope however to the best of our knowledge, there have not been any studies yet published studying the effect of latency on surgical performance in the setting of vitreoretinal surgery.

METHODS Thirty participants conducted two tasks, suturing and peeling, on a 3 dimensional heads-up display at 4 levels of latency, 50 ms, 66 ms, 90 ms, and 120 ms. For each time trial, the task completion time was measured. In addition a 6 item questionnaire on usability of the system was administered for each time trial. The order of the level of latency was randomized and blinded to the participant.

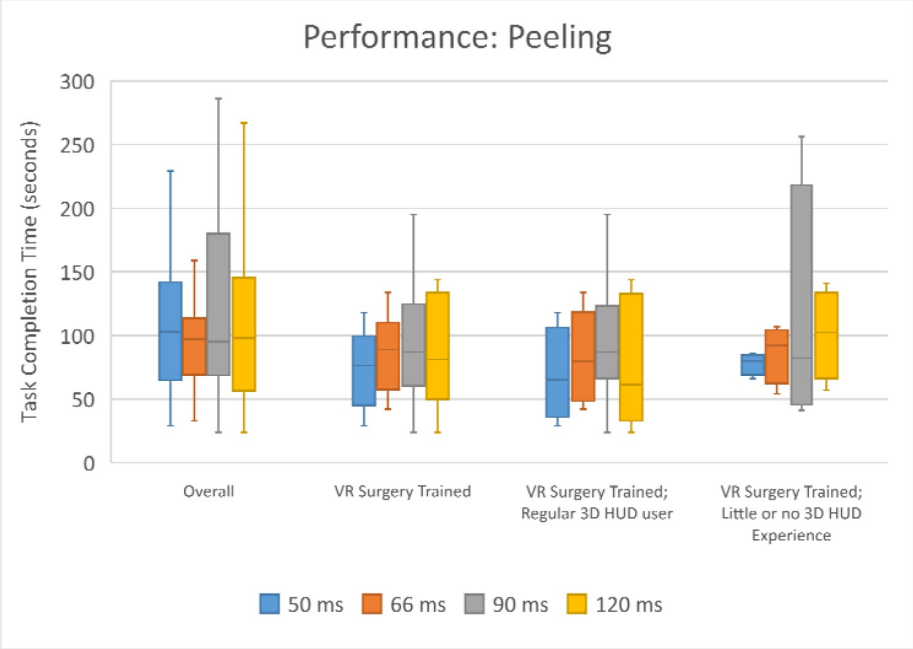
RESULTS In terms of surgical performance, for both the suture task and the peeling task, there was no statistical difference between completion times between a 50 ms latency and a 122 ms latency ($p=1.000$). This was also true when looking at the subgroups of participants who had VR training ($p=1.000$), and those who had VR training and regularly used 3D HUD ($p=1.000$). Usability of the system was measured by a 6 item questionnaire. In the suturing task, usability dropped by 60% at 122 ms when compared to 50 ms ($p<0.001$). This drop was also found in all subgroups as well. However, there was no statistical difference at 66 and 90 ms. In the peeling task, usability only dropped 20% at 122 ms compared to 50 ms ($p=0.12$) and this was also true for all the subgroups. None of these differences were statistically significant. Indeed, usability was not found to be significantly different at any of the latency values for the peeling task.

CONCLUSION The results of this study suggest that latency, at the levels found in current models of 3D HUD, are below the threshold of negatively affecting performance for the majority of users and therefore challenge the belief that latency plays a key role in the difference felt between the optical microscope and 3D HUD.

HUMAN RESEARCH Yes: Exempt from approval



Task completion time for the suturing task. None of the differences reached statistical significance.



Task completion time for the peeling task. None of the differences reached statistical significance.