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University of Maryland, School of Medicine
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Investigated long-term intraocular pressure (IOP) lowering effect of Femtosecond Laser Assisted Cataract Surgery (FLACS) vs. conventional phacoemulsification (PE).

June 2017 – December 2017
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Medical Student Researcher

Investigated the effect of Empagliflozin on cardiorespiratory fitness in patients with type II diabetes and reduced ejection fraction heart failure.

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July 2015 – July 2016 Bethesda, Maryland	**National Eye Institute (NEI)** **National Institutes of Health (NIH)** *Postbac IRTA* Investigated genetic cures for hereditary degenerative eye disease such as Retinitis Pigmentosa and Leber Congenital Amaurosis using CRISPR/Cas9 system.
June 2014 – May 2015 Richmond, California	**Sangamo Biosciences** **USA Dept. of Research & Development** *Research Intern* Conducted efficient high throughput screening for efficacious zinc finger nuclease therapeutics to specifically repress mutant huntington allele for treatment of Huntington disease.
December 2012 – May 2014 Berkeley, California	**University of California, Berkeley** **Professor David Schaffer's Laboratory** *Undergraduate Research Assistant* Examined neurotoxicity of Alzheimer's disease by generating various neuronal populations from fully undifferentiated human embryonic stem cells and analyzing cultures for the neurotoxicity of the Aβ oligomers. Completed a senior honors thesis by investigating the protective capacity of a novel 3D gel, which would allow efficient transplantation of dopamine neurons into the brains of Parkinson's patients.

Leadership Experience:

December 2016 – December 2017 Richmond, Virginia	**Medical Students for Choice (MSFC)** *Co-President* Involved in planning lunch lectures and practical workshops on topics such as contraception and family planning for medical students passionate about women's reproductive health. Encouraged advocacy and activism amongst the medical students on campus.
December 2016 - December 2017 Richmond, Virginia	**Vascular Surgery Interest Group** *Vice President* Involved in planning lunch lectures and information sessions for students interested in surgery and vascular surgery.

	Collaborate with other interest groups on campus to organize surgery focused career panels and seminars.
January 2013 – May 2014 Berkeley, California	**Planning to Achieve Collegiate Excellence (PACE)** *Vice President* Collaborated closely with school directors to schedule and conduct after school tutoring sessions. Trained tutors to provide local low-income middle school and high school students with free science and English tutoring services. Added a new section to the PACE program where we specifically assisted students with learning disabilities by using techniques such as paired reading. Designed and implemented training materials for tutors interested in working with students with learning disabilities.

Volunteering Experience:

March 2017 – June 2017 Richmond, Virginia	**Student Free Clinic at VCU** *Volunteer* Involved in providing free medical care to the uninsured population in Richmond, VA.
October 2017 - January 2018 Richmond, Virginia	**Autism Society Central Virginia** *Volunteer* Involved in holding teaching sessions for children with autism spectrum disorder and their families.
December 2012 – May 2014 Berkeley, California	**Woman and Youth Supporting Each other (WYSE)** *Volunteer Mentor* Participated in a year-long woman-only mentorship program dedicated to educating young women about various social and health topics ranging from healthy nutrition to STD prevention. Worked closely with program directors and other mentors to design a curriculum that helped middle school students learn about health-related topic through games, puzzles and other engaging activities.

Awards & Recognitions:

October 2011	Phi Theta Kappa
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Peer-reviewed Publications:

1. Zeitler B, Froelich S, Marlen K, Shivak DA, Yu Q, Li D, Pearl JR, Miller JC, Zhang L, Paschon DE, Hinkley SJ, Ankoudinova I, Lam S, Guschin D, Kopan L, Cherone JM, Nguyen HB, Qiao G**, Ataei Y**, Mendel MC, Amora R, Surosky R, Laganiere J, Vu BJ, Narayanan A, Sedaghat Y, Tillack K, Thiede C, Gärtner A, Kwak S, Bard J, Mrzljak L, Park L, Heikkinen T, Lehtimäki KK, Svedberg MM, Häggkvist J, Tari L, Tóth M, Varrone A, Halldin C, Kudwa AE, Ramboz S, Day M, Kondapalli J, Surmeier DJ, Urnov FD, Gregory PD, Rebar EJ, Muñoz-Sanjuán I, Zhang HS. Allele-Selective transcriptional repression of mutant HTT for the treatment of Huntington's disease. *Nat Med*. 2019;25(7):1131-1142. doi:10.1038/s41591-019-0478-3

2. Yu W, Mookherjee S, Chaitankar V, Hiriyanna S, Kim JW, Brooks M, **Ataeijannati Y**, Sun X, Dong L, Li T, Swaroop A, Wu Z. Nrl knockdown by AAV-delivered CRISPR/CAS9 prevents retinal degeneration in mice. *Nat Commun*. 2017;8(1):14716. doi:10.1038/ncomms14716

3. Vazin T, Ball KA, Lu H, Park H, **Ataeijannati Y**, Head-Gordon T, Poo MM, Schaffer DV. Efficient derivation of cortical glutamatergic neurons from human pluripotent stem cells: A model to study neurotoxicity of Alzheimer's disease. *Neurobiol Dis*. 2014;62:62-72. doi:10.1016/j.nbd.2013.09.005

Case Reports:

1. **Ataei Y**, Samara WA, Felton WL, Brar VS.
   Incomplete VKH in a 14 -Year-Old African American Female with Bilateral Disc Edema. (Manuscript submitted and under review)

Poster & Podium Presentations:

1. **Ataei Y**, Ong E, Betancourt A, Spagnolo B, Hammer A, Saeedi O.
   Long term intraocular pressure (IOP) lowering effect of Femtosecond Laser Assisted Cataract Surgery (FLACS) versus conventional phacoemulsification (PE).
   ARVO Annual Meeting, Baltimore, Maryland; May 2020. (Meeting cancelled due to COVID-19 pandemic)

2. Trankle C, **Ataei Y**, Christopher A, Kadariya D, Johnson JL, Vo C, Schatz A, Park TS, Mankad P, Carbone A, Canada J, Buckley L, Markley R, Kontos M, Arena R, Van Tassell B, Abbate A.

Interleukin-1 Blockade in Heart Failure with Preserved Ejection Fraction: The Diastolic Heart Failure Anakinra Response Trial-2 (D-HART2).
VCUSOM Research Day, Richmond, Virginia; April 2018.

3. Amendola M. **Ataei Y.**
Native Arteriovenous Fistula (NAVF) Infections: Case Report and Review of Literature.
Society of Clinical Vascular Surgery- 46th Annual Symposium on Vascular Surgery, Las Vegas, Nevada; March 2018.

4. **Ataei Y**, Amendola M**.**
Native Arteriovenous Fistula (NAVF) Infections: Case Report and Review of Literature**.**
Virginia Vascular Surgical Society, Williamsburg, Virginia; September 2017.

5. Mookherjee S, Yu W, Hiriyanna S**, Ataeijannati Y**, Li T, Swaroop A, Wu Z.
A CEP290 C-terminal protein fragment rescues retinal degeneration in a mouse model of Leber Congenital Amaurosis.
ARVO Annual meeting, Baltimore, Maryland; May 2017.

6. Yu W, Mookherjee S, Kim JW, Hiriyanna S**, Ataeijannati Y**, Sun X, Dong L, Li T, Swaroop A, Wu Z.
In vivo reprogramming of rods to cone-like cells by *Nrl*-knockdown using AAV-delivered CRISPR-Cas9 rescues retinal degeneration.
ARVO Annual Meeting, Seattle, Washington; September 2016.

7. **Ataeijannati Y**, Vazin T, Conway A, Schaffer D.
Development of defined systems for generation and transplantation of human dopaminergic neurons.
UC Berkeley Molecular and Cell Biology Honors Poster Presentation, Berkeley, California; April 2014.

8. **Ataeijannati Y**, Vazin T, Conway A, Schaffer D.
Development of defined systems for generation and transplantation of human dopaminergic neurons.
SSSCR conference: Culturing a Stem Cell Community, Berkeley, California; October 2014.

Other Publications:

Ataei Y. July 18, 2017.
Association of American Medical Colleges, Inspiring Stories
(In a collaboration with AAMC, I published an article featuring my journey through medical school admission as a new immigrant)
https://students-residents.aamc.org/choosing-medical-career/article/yasaman-ataei/

Abstract

Title: Long term intraocular pressure (IOP) lowering effect of Femtosecond Laser Assisted Cataract Surgery (FLACS) versus conventional phacoemulsification (PE)

Yasaman Ataei, Master of Science, 2020

Dissertation directed by: Osamah Saeedi, MD, MS, Associate Professor of Ophthalmology & Jessica Brown, PhD, Assistant Professor of Epidemiology and Public Health

This is a retrospective cohort study of 244 otherwise healthy eyes (from 244 patients) undergoing cataract surgery. Patients were followed postoperatively at 1, 3, 6, 12, 24, 36 months for IOP measurement. Combination procedures and glaucomatous eyes were excluded. 147 eyes underwent conventional phacoemulsification and 97 underwent FLACS. Amongst eyes undergoing FLACS, we observed 1.42 mmHg crude decrease in postoperative IOP from baseline over 3 years of follow-up ($p = 0.003$). Amongst eyes undergoing conventional phacoemulsification, we observed 1.18 mmHg crude decrease in postoperative IOP from baseline over 3 years of follow-up ($p = 0.003$). Amongst non-Caucasian patients, eyes undergoing FLACS had 1.90-3.38 mmHg lower postoperative IOP compared to eyes undergoing conventional phacoemulsification (ps = 0.04-0.009). Our study showed that in non-Caucasian patients who were followed for an average of 22 months, the postoperative IOP was significantly lower in eyes that underwent FLACS compared to eyes that underwent conventional phacoemulsification.

Long term intraocular pressure (IOP) lowering effect of Femtosecond Laser Assisted Cataract Surgery (FLACS) versus conventional phacoemulsification (PE)

by
Yasaman Ataei

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CDE	Cumulative Dissipated Energy
EMGT	Early Manifest Glaucoma Trial
FLACS	Femtosecond Laser Assisted Cataract Surgery
GAT	Goldmann applanation tonometry
HIPAA	Health Insurance Portability and Accountability Act
IOL	Intraocular Lens
IOP	Intraocular Pressure
LASIK	Laser-Assisted In Situ Keratomileusis
LP	Lens Position
NCOA	National Council on Aging
NCT	Non-Contact Tonometer
OBF	Ocular Blood Flow tonometer
PACG	Primary Angle Closure Glaucoma
RLP	Relative Lens Position
UMMC	University of Maryland Medical Center
WHO	World Health Organization
XFS	Exfoliation Syndrome

CHAPTER 1

Introduction & Background

What is a cataract?

Cataract is a disease where the clear crystalline lens in the eye becomes opacified[1,2]. In a healthy eye, this lens is a clear structure suspended from zonular fibers and is primarily responsible for refracting light and forming a clear image on the retina[1,2]. Several risk factors, such as smoking and ultraviolet radiation exposure, have been associated with increased risk of cataract development[1,3]. However, natural aging remains the most common cause of cataract formation[1,2]. Regardless of the cause, the definitive treatment for a visually significant cataract is surgery[1].

What is a cataract surgery?

Cataract surgery is one of the most common operations performed in hospitals around the world and the prevalence is expected to increase as the aging population grows[4]. Currently, around 3 million patients undergo cataract surgery in the United States each year[5]. The first method of performing cataract surgery back in the fifth century BC was called couching[1]. This procedure mainly consisted of dislodging the lens out of the visual axis instead of removing it[1]. Despite significant visual improvement achieved immediately after the surgery, the procedure was often accompanied by devastating complications such as severe infection leading to blindness[1].

Since then, there have been numerous advances. The field was truly transformed in 1976 with the introduction of phacoemulsification by Charles Kelman – an American ophthalmologist[6]. Conventional phacoemulsification is currently the standard surgical procedure for cataract removal, where ultrasound energy is used to break up and emulsify the lens before extraction via irrigation and suction[4,7]. The surgery typically starts with a small corneal incision (1.8 mm to 2.75 mm)[1]. Subsequently, a small opening is made into the anterior lens capsule via circular motion – a step known as capsulorrhexis[1]. A phacoemulsification device is then inserted which delivers ultrasound energy to emulsify and aspirate the opacified lens[1]. The remaining capsular bag will then host the new intraocular lens (IOL)[1]. Despite the complexity of the procedure, an experienced surgeon is able to perform the above steps with great consistency and achieve predictable results the majority of the time[1].

What is Femtosecond Laser Assisted Cataract Surgery (FLACS)? What are its advantages over conventional phacoemulsification?

With constant push for improvement, Femtosecond Laser Assisted Cataract Surgery (FLACS) was introduced for the first time in 2008[1]. Prior to its use in cataract surgery, femtosecond laser technology had been used in laser assisted in-situ keratomileusis (LASIK) surgery since 2001[1]. The success of femtosecond laser in LASIK surgery was mainly due to its ability to create precise corneal flaps[1]. The precision, predictability and reproducibility of this new technology were thought to be beneficial in cataract surgery[1]. Therefore, FLACS was introduced to cataract surgery where a femtosecond laser is used to perform precise corneal incisions, capsulorrhexis and lens fragmentation[1].

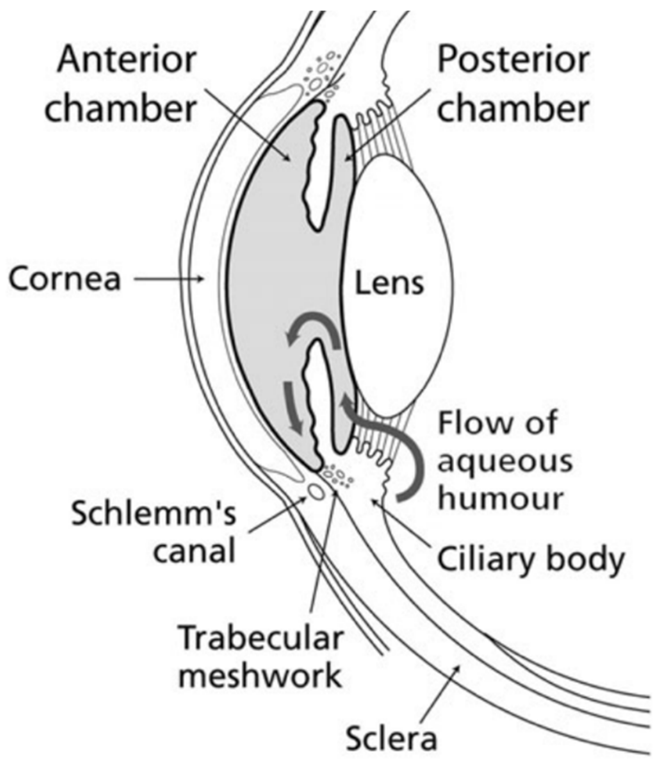
The ability to perform precise capsulorrhexis was believed to facilitate IOL implantation leading to better refractive and visual outcomes[1,8]. However, a recent retrospective cohort study on 1838 eyes by Berk et al. showed that there was no statistically significant difference in the refractive outcome of eyes undergoing FLACS compared to eyes undergoing conventional phacoemulsification[9]. A retrospective cohort study on 735 eyes by Ang et al. also failed to find any statistically significant difference between FLACS and conventional phacoemulsification in terms of visual outcomes[10].

Although the use of a femtosecond laser to fragment the lens does not completely eliminate the use of ultrasound energy, this pretreatment with laser is believed to lower the total ultrasound energy used during the surgery[8]. There are several studies that showed a statistically significant reduction in ultrasound energy during the surgery in FLACS versus conventional phacoemulsification[11,10,12]. Reduced use of ultrasound energy is one of the most important advantages of FLACS since ultrasound energy is known to cause heat-induced damage to ocular structures resulting in undesirable long-term complications such as macular edema or corneal endothelial cell loss[13,14]. These findings suggest that perhaps FLACS is most beneficial in patients with a highly dense cataract or pre-existing corneal endothelial defects[8].

What is intraocular pressure and how is it regulated?

The pressure inside the eye is referred to as intraocular pressure (IOP) and it ranges from 10-20 mmHg in a healthy eye[15]. IOP within this normal range is necessary for maintaining normal eye anatomy as well as good refraction[15]. The human eye is a relatively rigid sphere where the volume of its contents directly regulates the pressure inside[15]. The regulation of IOP in the human eye is primarily achieved through the regulation of aqueous humor volume in the anterior chamber[15]. Aqueous humor is produced by a structure known as ciliary bodies[15]. Once produced in the posterior chamber, aqueous humor flows over the lens, passes around the iris and finds its way into the anterior chamber (Figure 1)[15]. From the anterior chamber, the majority of the aqueous humor drains through the trabecular meshwork and Schlemm's canal located at the angle between iris and cornea (Figure 1)[15]. Chronic IOP elevation often leads to irreversible damage to the optic nerve and loss of visual field[15].

Figure 1, Aqueous humor pathway in the eye



(Image borrowed from "Intraocular pressure" by Murgatroyd H, Bembridge J.[15])

How does cataract surgery affect postoperative IOP?

It is well established that conventional phacoemulsification can lead to a postoperative IOP reduction[16,17,18]. However, despite overwhelming evidence, the exact mechanism behind this observed effect is not well understood. One hypothesis states that removal of the opacified lens and replacing it with a much thinner intraocular lens (IOL) leads to the deepening of the anterior chamber[19,20]. Consequently, the angle between the iris and cornea becomes wider, aqueous humor outflow improves and IOP is decreased[19,20]. An alternative hypothesis suggests that removal of the crystalline lens allows the lens capsule to move posteriorly and pull back zonular fibers and ciliary processes[21]. These changes, in turn, will widen the Schlemm's canal, improve aqueous humor outflow and lower the IOP[21]. Additionally, this traction on the zonules could lead to decreased aqueous humor production and lower the IOP[22]. Another hypothesis suggests that the ultrasound energy used during the surgery is the main reason behind the IOP lowering effect through two primary mechanisms:

- Ultrasound-induced remodeling of the trabecular meshwork, which leads to improved outflow, an effect similar to laser trabeculoplasty [21,18,23]
- formation of free radicals leading to reduced aqueous humor production[21].

In fact, Fernandez-Barrientos and colleagues conducted a fluorophotometry study and discovered a 46% increase in trabecular aqueous outflow after the cataract surgery providing more evidence for improved outflow being one of the key mechanisms behind the IOP lowering effect observed[24].

Conceptual Framework

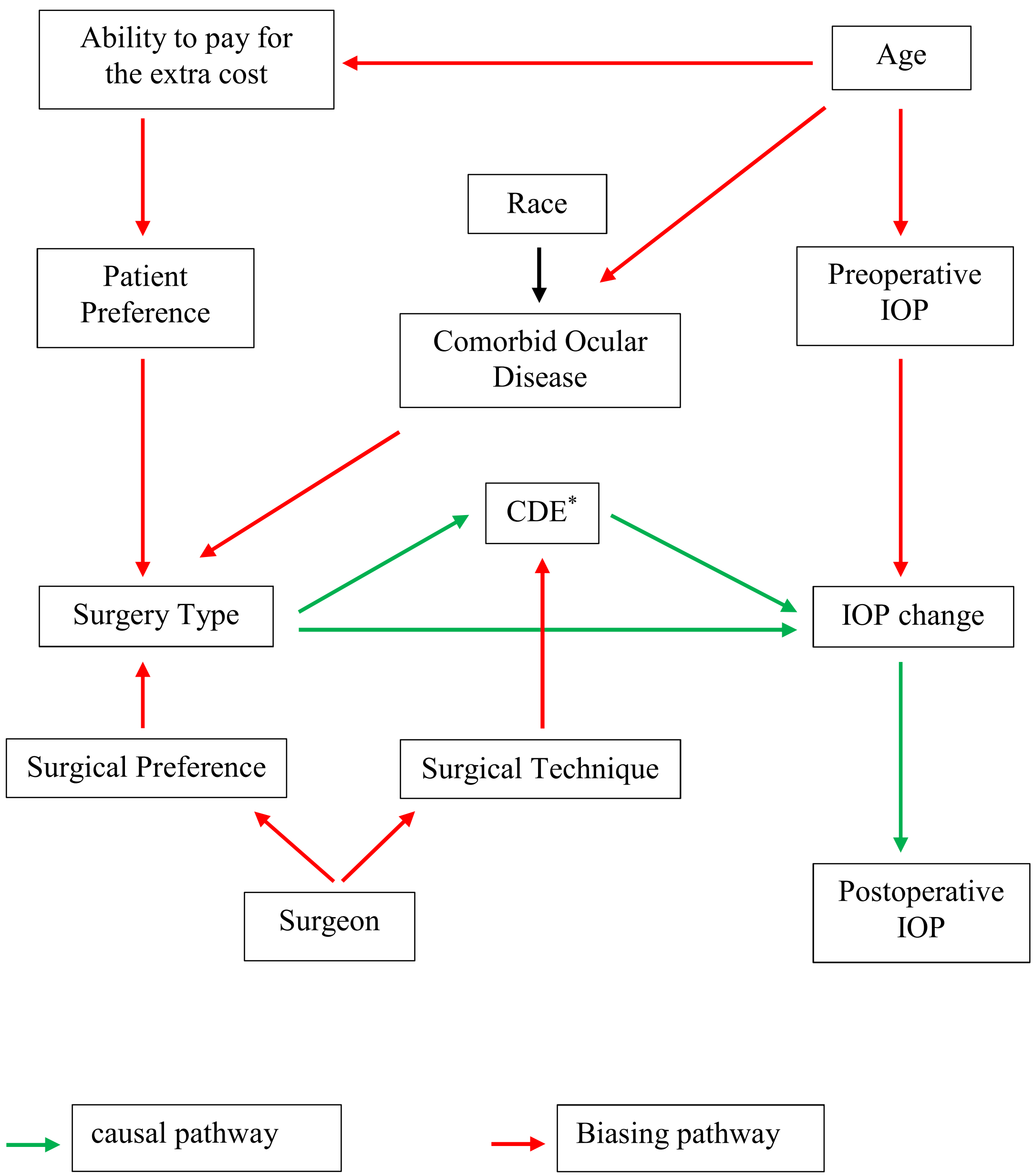
Several factors can affect the relationship between our study exposure (surgery type: conventional phacoemulsification vs. FLACS) and the outcome (postoperative IOP). Understanding what these factors are and how they interact with our exposure and outcome will help us have a conceptual framework going into this study.

Currently, patients receiving cataract surgery in the United States have a median age of 65 years[25]. According to the National Council of Aging (NCOA), 25 million American adults ages 60 years and above experience economic insecurity[26]. This lower economic status may affect the patient's ability to pay for the extra cost associated with FLACS. Therefore, older patients might be more likely to choose conventional phacoemulsification over FLACS when presented with the option. It is also known that older age is associated with higher IOP[27]. Given that the higher preoperative IOP has been shown to be the biggest predictor of the reduction in postoperative IOP[28], adults with older age and higher preoperative pressure are expected to experience a bigger reduction in their IOP after surgery. Finally, older age predisposes patients to the development of certain ocular comorbidities (such as glaucoma and retinal disorders)[29] which, in turn, can influence the choice of surgery type[30]. As a result, age has the potential to act as a confounder in our study.

Another key element in this conceptual framework is race and its interaction with the exposure. It is well known that race is linked to the presence of certain ocular comorbidities[31]. For instance, according to the data from the National Eye Institute, African Americans have a significantly higher prevalence of glaucoma compared to other races[32]. There are also known differences in terms of ocular anatomy between the races[33,34,35]. For instance, Asians have a more anterior iris root insertion compared to other racial groups[35,33]. This insertion is the most posterior in Caucasians and differences in angle architecture are the hypothesized cause of Asians predisposition to primary angle-closure glaucoma (PACG)[35,33]. We suspect these anatomical variations could make race a potential effect modifier in our study.

Finally, surgeons play a key role in determining which patient receives what type of surgery. When deciding if a patient is a good candidate for FLACS, a surgeon carefully looks for any contraindication for FLACS[30]. One of the most common contraindications is the presence of ocular comorbidities, such as severe glaucoma or retinal vascular disease[30]. This decision-making process introduces confounding by indication and should be addressed as much as possible. Additionally, each surgeon might use a slightly different technique during the surgery or might have a personal preference for one surgery type over another. Therefore, the surgeon can act as a confounder in our study. Figure 2 is a summary of all the potential relationships described above.

Figure 2, Directed Acyclic Graph demonstrating pathways between surgery type and postoperative IOP:



*Cumulative dissipated energy (**CDE**) is the amount of ultrasound energy used during the surgery.

Literature Review

In this section, we will review a select number of previous literature where the IOP reduction after conventional phacoemulsification or FLACS was investigated.

In 2001, Pohjalainen and colleagues conducted a prospective cohort study investigating the change in IOP after conventional phacoemulsification in non-glaucomatous eyes with and without exfoliation[36]. The study included 160 eyes (23 eyes with exfoliation and 137 without it) that underwent phacoemulsification with IOL implantation and were followed over time for IOP changes at 1 day, 1 week, 4 months, 1 year and 2.7 years postoperatively[36]. In eyes with exfoliation, the postoperative IOP decreased by 3.8 ± 2.3 mmHg from baseline after 1 to 2.7 years of follow-up (Wilcoxon and t-test)[36]. In eyes without exfoliation, this decrease in postoperative IOP was also 3.8 ± 15.9 mmHg from baseline over the same length of follow-up (Wilcoxon and t-test)[36]. Although the drop in IOP postoperatively was statistically significant within each group, there was no statistically significant difference between the groups (Wilcoxon-2-sample and t-test)[36]. The findings of this study provided critical information demonstrating the significant IOP lowering effect of phacoemulsification both immediately after surgery and over a long term follow-up period[36]. This study also identified a correlation between phacoemulsification time and the IOP lowering effect of conventional phacoemulsification (spearman correlation)[36]. The author ended the paper by hypothesizing that the decrease in aqueous humor production is most likely the explanation behind the long-term IOP lowering effect observed after conventional phacoemulsification[36].

In 2008, Poley and colleagues conducted a retrospective review of 588 eyes (81 eyes with ocular hypertension and 507 normotensive eyes) undergoing conventional phacoemulsification and IOL implantation[37]. Patients were followed for up to 10 years postoperatively, where 97% of them had at least 1 year of postoperative follow-up and only 8% had 9-10 years of follow-up[37]. The study found that patients with the most elevated preoperative IOP (23-31 mmHg) experienced on average 6.5 ± 2.8 mmHg drop in their postoperative pressure from baseline[37]. On the other hand, patients with the lowest preoperative IOP (9-14 mmHg) experienced as little as 0.2 ± 2.6 mmHg increase in their postoperative pressure from baseline[37]. Additionally, while all patients with preoperative pressure of 23-31 mmHg experienced IOP reduction postoperatively, only 55% of the patients with preoperative IOP of 9-14 mmHg had a decrease in postoperative pressure and 45% actually experienced an increase[37]. This study also compared the IOP reduction from baseline amongst eyes with ocular hypertension (preoperative IOP ≥ 20 mmHg) versus eyes with normal ocular pressure (preoperative IOP ≤ 19 mmHg)[37]. This comparison showed that eyes with ocular hypertension (81 eyes) experienced 5.5 ± 3.1 mmHg decrease in IOP at 1 year follow-up and this decrease was sustained at 5.2 ± 2.8 mmHg through their last available follow-up period[37]. Normotensive eyes (507 eyes), however, only experienced 0.9 ± 2.9 mmHg decrease in IOP at 1 year and this decrease was also sustained at 1.1 ± 2.5 mmHg through their last available follow-up point[37]. Finally, this decrease in IOP postoperatively was independent of the age at the time of surgery and patients in all age groups were equally likely to experience a reduction in the IOP postoperatively[37]. All of the above findings suggested that the preoperative IOP was the main predictor of the IOP lowering effect observed after conventional phacoemulsification[37]. Interestingly, out of 81 eyes with ocular hypertension prior to the surgery, 60 eyes (74%) turned normotensive at their final follow up point meaning their ocular hypertension was cured after conventional phacoemulsification[37].

In 2006, Damji et al. conducted a prospective multicenter cohort study comparing the IOP lowering effect of conventional phacoemulsification in patients with exfoliation syndrome (XFS) to patients without exfoliation syndrome (non-XFS)[38]. The study recruited 71 subjects with exfoliation (42 with exfoliation syndrome and 29 with exfoliative glaucoma) and 112 subjects without exfoliation syndrome (83 with otherwise healthy eyes and 29 with glaucoma)[38]. All patients underwent phacoemulsification with IOL placement and their postoperative IOP was measured at 1 day, 1 week, 3 week, 6 week, 6 month, 1 year and 2 year time points[38]. Reduction in postoperative IOP was compared between the two cohorts at all time points using a multivariable linear regression model which accounted for the highest preoperative IOP and irrigation volume[38]. A similar analysis was done for all subgroups where IOP reduction in the exfoliation syndrome subgroups was compared to IOP reduction in exfoliative glaucoma, glaucoma patients and healthy controls using the same linear regression model[38]. The results showed that IOP reduction after conventional phacoemulsification was significantly greater in patients with exfoliation syndrome after 2 years of follow-up (reduction was 2.51 ± 3.70 mmHg in XFS cohort versus 0.89 ± 3.51 in the non-XFS cohort, p-value = 0.01)[38]. The postoperative IOP reduction in healthy eyes over 1 year and 2 year follow-up was 0.84 ± 0.42 mmHg and 0.62 ± 0.42 mmHg respectively[38]. The linear regression model also demonstrated that the biggest predictors of the IOP reduction after surgery were the presence of exfoliation, irrigation volume and preoperative IOP[38]. Damji et al. concluded that patients with exfoliation syndrome experienced a greater IOP reduction after cataract surgery compared to patients without exfoliation and the degree of reduction was highly correlated with the irrigation volume[38].

In 2011, Samuelson et al. conducted a randomized open-label controlled trial in 240 patients with mild to moderate open-angle glaucoma[39]. Out of this number, 122 patients were randomized to receive cataract surgery only (control group) and 111 were randomized to receive cataract surgery combined with iStent implantation (intervention group)[39]. The preoperative IOP was measured in all subjects while they were on their IOP lowering medications[39]. All subjects subsequently underwent a washout period appropriate for their medication regimen prior to the surgery[39]. The mean medicated preoperative IOP was 18.4 ± 3.2 mmHg and the mean unmedicated preoperative IOP was 25.4 ± 3.6 mmHg[39]. After the surgery, postoperative IOP was measured at 1 day, 1 week and 3, 6, 12, 18 and 24 month time points[39]. Comparing the postoperative IOP at the 12 month follow-up to the unmedicated baseline IOP (t-test) showed that the control group experienced 8.5 ± 4.3 mmHg IOP reduction and the intervention group experienced 8.4 ± 3.6 mmHg IOP reduction[39]. Comparing the postoperative IOP at 12 month follow-up to the medicated baseline IOP (t-test) showed that the control group experienced 1.0 ± 3.3 mmHg IOP reduction and the intervention group experienced 1.5 ± 3.0 mmHg IOP reduction[39]. The results indicated that the reduction in postoperative IOP was similar between the two groups but the intervention group achieved this IOP reduction with less hypotensive medications[39].

Clearly, the IOP lowering effect of phacoemulsification has been established and investigated in a wide range of patients. The IOP lowering effect following FLACS, however, is less well known. A recent randomized control trial by Roberts et al. in the UK compared FLACS to conventional phacoemulsification in terms of various clinical outcomes[40]. The study enrolled a total of 400 healthy eyes equally distributed between the FLACS and conventional phacoemulsification arms[40]. One of the outcomes investigated was the change in postoperative IOP from baseline to 1 month after the surgery [40]. This study found no statistically significant difference in IOP change between FLACS and phacoemulsification at 1 month after the surgery (t-test)[40]. While these findings are valuable, the author did not provide any concrete data on the postoperative IOP change in FLACS or conventional phacoemulsification. The findings of this study are also limited by the short follow-up time and it does not provide any information on the long term IOP lowering effect of FLACS.

To our knowledge, the most extensive study investigating the IOP lowering effect of FLACS is a multicenter retrospective cohort study by Shah et al. in 2019 [41]. This study aimed to assess the long-term effect of FLACS on postoperative IOP in glaucomatous eyes versus healthy (control) eyes[41]. There were a total of 504 eyes enrolled in the study, 226 were healthy eyes and 278 were glaucomatous[41]. All patients enrolled in the study underwent FLACS and were followed for 3 years postoperatively and assessed primarily for changes in IOP both immediately after the surgery (at postoperative day 1 and week 1) and later on (at postoperative 1, 3, 6, 12, 24 and 36 months)[41]. Shah et al. found that both healthy eyes and glaucoma/glaucoma suspect eyes experienced a statistically significant increase in IOP immediately after the surgery at 1 day after the surgery[41]. The IOP subsequently returned to baseline at 1 week and showed a significant decline from baseline at 1 month for both cohorts[41]. This statistically significant decline in IOP from baseline persisted until 1 year after the surgery for the healthy eyes and up to 3 years after the surgery for glaucoma/glaucoma suspect eyes[41]. Compared to healthy eyes, eyes with glaucoma experienced a greater increase in IOP from baseline to day 1 and a greater decline in IOP from baseline to 1, 2 and 3 year time points[41]. Interestingly, this study found no significant correlation between change in IOP at one year and the intraoperative cumulative dissipated energy (CDE)[41]. Shah et al. concluded that this finding suggests that ultrasound energy is perhaps not the only factor responsible for the IOP lowering effect in FLACS[41].

Current Gap in Knowledge

To our knowledge, there is currently only one study that investigated the IOP lowering effect of FLACS[41]. Despite all the facts known about the refractory outcome, safety and efficacy of this newer technology[9,10,40], very little is known about its IOP lowering effects. In fact, there are currently no studies directly comparing the long-term IOP lowering effect of FLACS to conventional phacoemulsification. Therefore, we aim to address this gap in knowledge by conducting the current study to compare postoperative IOP in healthy eyes undergoing FLACS versus conventional phacoemulsification over 3 years of follow-up.

Clinical Significance

During this study, we hope to answer the following question: does conventional phacoemulsification with IOL placement lead to lower postoperative IOP compared to FLACS with IOL placement? This is an important research question that could affect clinical decision-making, especially when it comes to performing cataract surgery on patients with elevated IOP prior to cataract surgery. If one technology proved to be significantly more effective at lowering IOP postoperatively, surgeons might choose that surgical technology for patients who could benefit from IOP reduction after the surgery. Additionally, the exact mechanism behind the IOP lowering effect after cataract surgery is still not entirely known. Therefore, if we find a significant difference between the two surgery types concerning their IOP lowering properties, we may have a more precise understanding of the mechanism behind this observed effect.

Study Aims

Study aim 1:

To compare the baseline characteristics between the two study groups (conventional phacoemulsification versus FLACS) and identify any presurgical variables which are significantly different between these two groups.

Study aim 2a:

To compare the change from preoperative to postoperative IOP among eyes which received conventional phacoemulsification and those which received FLACS. This will be done for each follow-up time point.

Study aim 2b:

To compare the postoperative IOP between eyes which received conventional phacoemulsification and those which received FLACS, separately at each follow-up time point.

Study aim 3:

Use a linear regression model to determine if conventional phacoemulsification is associated with a larger reduction in postoperative IOP than FLACS. We will control for preoperative IOP (the most important predictor of postoperative pressure)[37] and time to last follow-up in this regression model. Additionally, we will consider other potential confounders such as age, gender, surgeon, eye side, and eye sequence. Finally, we will investigate the possibility of effect modification by race category, an *a priori* potential effect modifier based on previous evidence indicating ocular anatomical differences between races[33,34].

Hypothesis

We hypothesize that healthy eyes undergoing conventional phacoemulsification cataract surgery will have a lower postoperative IOP compared to those undergoing Femtosecond Laser Assisted Cataract Surgery (FLACS).

CHAPTER 2

Methods

Study design

We conducted a single-center retrospective cohort study of healthy eyes undergoing cataract surgery between February 1st, 2014 and December 31st, 2015 at an ambulatory ophthalmology surgical center affiliated with a private practice in Glen Burnie, Maryland. An ophthalmology resident trained in HIPAA at UMMC collected patient information on all the study variables using electronic medical records. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Maryland. The dataset was de-identified prior to any analysis to comply with HIPAA requirements.

Subject Selection and Data Cleaning

2002 cataract surgeries were identified in the study period using the same population and inclusion criteria of our prior study by Saeedi et al.[12]. A sample of consecutive patients with the longest follow-up time was selected. This sample was balanced by the practitioner to include a representative number of surgeries performed by each surgeon. All eyes in this sample were then screened by a more stringent exclusion criteria as described below.

To be included in the study, an eye must have:

- belonged to a subject who was 18 years or older at the time of surgery
- had its type and date of surgery listed
- had at least one preoperative IOP and one postoperative IOP measurement.

We excluded any eyes with:

- missing key patient demographic information (age, race and gender)
- missing intraoperative information (such as lens type)
- history of glaucoma
- history of IOP lowering medication use
- history of corneal disease (keratoconus)
- history of vitrectomy/retinal repair
- atypical ocular anatomy (i.e. history of narrow angle or traumatic cataract).
- cataract surgery combined with other intraocular procedures (i.e. pterygium removal)
- cataract surgery complicated with concurrent vitrectomy.

Eyes with a diagnosis of glaucoma are often on IOP lowering medication, which lowers their eye pressure[42]. In addition, vitrectomy (removal of the vitreous humor) is known to affect IOP postoperatively[43,44]. Therefore, excluding glaucomatous eyes as well as eyes with current or previous vitrectomy from the study should ensure that any observed IOP lowering effect was due to the cataract surgery itself and no other concurrent interventions. Additionally, some corneal diseases (such as keratoconus) could interfere with accurate IOP measurements[45], and therefore these eyes were also excluded from the study.

Our dataset included several subjects who received cataract surgery on both eyes. For these subjects, we chose to include only the first eye undergoing surgery in the statistical analyses. It is critical to note that the first eye undergoing cataract surgery tends to be the eye with a more visually significant cataract[46]. Therefore, to ensure that our choice to analyze the first eye only did not introduce any selection bias, we performed a sensitivity analysis. This analysis was performed by analyzing a dataset that included only the second eye undergoing surgery for those who had surgery done on both eyes.

Study Variables

The outcome variable used to meet aims 2a and 2b (t-test) in this study was different from the outcome variable used for aim 3 (linear regression).

The outcome variable for aims 2a and 2b is the postoperative IOP (mmHg) measured at 6 distinct time points (1, 3, 6, 12, 24 and 36 months) following cataract surgery. The IOP measurement at 1 month after the surgery was taken from the one-month postoperative note since this is a routine postoperative visit for all cataract surgeries. For other follow-up points (3, 6, 12, 24 and 36 months), which are not routine post-surgery appointments, a two-month window (one month before and one month after) around the expected follow-up time was used to record the IOP measurements. For instance, to record the postoperative IOP at 3 months visit, we looked for any notes written between 2-4 months after the surgery to obtain the IOP measurement for this time point. The outcome variable for aim 3 is each individual's postoperative IOP (mmHg) measured at their last follow-up time point. Postoperative IOP is a continuous variable.

The main exposure of interest for all study aims is a binary indicator variable for the type of cataract surgery that the patient received - conventional phacoemulsification vs. FLACS.

Patient demographic information included in this study are age in years at the time of surgery, sex and race (Caucasian, African American, other). All eyes which were not from Caucasian or African American patients were included in the “other” race category and no further information on the specific race of these eyes was collected. Age is a continuous variable; sex is binary, and race is categorical. Pertinent intraoperative variables included in the study are eye side (the cataract surgery was performed on the right vs. left eye), eye sequence (the first eye undergoing cataract surgery vs. the second eye) and surgeon (a categorical indicator variable with three levels for the three surgeons who performed the surgeries). Eye side and eye sequence are binary variables. Surgeon is a categorical variable. Pertinent baseline characteristics included in this study are mean preoperative IOP (measured in mmHg and consisting of the average of the 1-3 IOP measurements recorded within the one year prior to the surgery). Preoperative IOP is a continuous variable.

Finally, for the linear regression model (aim 3), month to follow-up was defined as the month the last IOP measurement was obtained. For instance, if a subject had their last IOP measured at 36 months, the month-to-follow-up corresponding to that IOP was 36.

Statistical Analysis

We compared the baseline and intraoperative characteristics of the two groups (FLACS vs. conventional phacoemulsification) using t-tests for continuous variables (age and average preoperative IOP) and chi-square tests for categorical and binary variables (gender, race, eye side, eye sequence and surgeon). If the expected number of eyes was less than 5 in any of the chi-square test cells, then the Fishers exact test was used.

To account for confounding by indication, we excluded all eyes with glaucoma from the study prior to the data analysis. Additionally, we compared the distribution of surgery type between surgeons using a chi-squared test to detect any fundamental differences between surgeons' preference for one surgery type over the other.

A paired t-test was used to compare the postoperative IOP to preoperative IOP of eyes undergoing conventional phacoemulsification and those undergoing FLACS at each follow-up time point. An unpaired t-test was used to compare the postoperative IOP of eyes in each surgery group (conventional phacoemulsification vs. FLACS) at each follow-up time point.

To compare the long-term IOP lowering effect of FLACS to conventional phacoemulsification, a linear regression model was used. In this model, the last measured postoperative IOP was the primary outcome and the type of surgery (FLACS vs. conventional phacoemulsification) was the primary exposure while accounting for average preoperative IOP and time to follow-up. This approach was chosen as not all eyes have postoperative IOP measurements at each time point, but this would allow us to maximize the number of eyes included in the analysis. To examine potential confounding by patient baseline demographics and intraoperative measurements, we performed a multivariable analysis including each potential variable (age, gender, eye side, eye sequence, and surgeon) into the linear model one at a time and keeping only the ones which had a p-value < 0.1. We then considered the possibility of effect modification of the surgery type on the outcome by race by including the interaction between race and the exposure and assessing the type III test of the overall interaction term, using the same p-value of 0.1 to determine if the interaction was retained.

All analyses were performed using SAS University version 9.4. For all hypothesis tests, a p-value less than 0.05 was considered statistically significant.

CHAPTER 3

Results

Out of the selected sample described in the methods section, 371 eyes met the inclusion criteria. Among these surgeries, there were 59 subjects who received cataract surgery on both eyes (23 of them received FLACS on both eyes and 36 of them received conventional phacoemulsification on both eyes). Eliminating eyes which met the exclusion criteria and only taking the first eye from subjects with surgery done on both eyes, brought our final sample size to 244 eyes (from 244 independent patients). We conducted our final analyses on these 244 eyes. Details about the number of eyes excluded during data cleaning are listed in Appendix 1. Conventional phacoemulsification was used on 147 (60.3%) eyes and 97 (39.7%) eyes received FLACS. There was no statistically significant difference in the mean age of those who received FLACS versus those who received conventional phacoemulsification (67.74 ± 9.30 compared to 69.92 ± 9.04 years, p-value = 0.07). Out of 244 eyes in the study, 186 eyes (76.2%) had one preoperative IOP measurement, 30 eyes (12.3%) had two preoperative IOP measurements and 28 eyes (11.5%) had three preoperative IOP measurements. The mean preoperative IOP was 16.06 ± 2.90 mmHg in eyes undergoing conventional phacoemulsification and 16.23 ± 2.49 mmHg in eyes undergoing FLACS. There was no statistically significant difference in preoperative IOP between the two groups (p-value = 0.65). Finally, the eyes undergoing FLACS were similar to eyes undergoing conventional phacoemulsification with respect to all other baseline characteristics, including sex, race, eye side, eye sequence and surgeon (Table 1).

Table 1, Baseline Patient Characteristics:

	Total N = 244	**Conventional PE N = 147 (60.3%)**	**FLACS N = 97 (39.7%)**	**p-value [1]**
Mean Age (years) ± SD	69.05 ± 9.19	69.92 ± 9.04	67.74 ± 9.30	0.07
Sex N (%)				
Female	147 (60.2%)	92 (62.6%)	55 (56.7%)	
Males	97 (39.8%)	55 (37.4%)	42 (43.3%)	0.36
Race N (%)				
Caucasian	206 (84.4%)	120 (81.6%)	86 (88.7%)	
African American	26 (10.7%)	19 (12.9%)	7 (7.2%)	0.31
Other	12(4.9%)	8 (5.4%)	4 (4.1%)	
Eye Side N (%)				
Right	112 (45.9%)	60 (40.8%)	52 (53.6%)	0.05
Left	132 (54.1%)	87 (59.2%)	45 (46.4%)	
Eye Sequence N (%):				
First	168 (68.9%)	99 (67.3%)	69 (71.1%)	0.53
Second	76 (31.1%)	48 (32.7%)	28 (28.9%)	
Mean Preoperative IOP (mmHg) ± SD:	16.13 ± 2.74	16.06 ± 2.90	16.23 ± 2.49	0.65
Surgeon N (%):				
Surgeon 1	56 (23.0%)	33 (22.4%)	23 (23.7%)	
Surgeon 2	44 (18.0%)	29 (19.7%)	15 (15.4%)	0.70
Surgeon 3	144 (59.0%)	85 (57.8%)	59 (60.8%)	

[1] p-value comparing conventional phacoemulsification to FLACS group
[*]Statistically significant result at $p < 0.05$

Amongst eyes that received conventional phacoemulsification, there was a statistically significant decrease in IOP from preoperative to postoperative at the 1, 6, 12, 24, and 36 months follow-up time points. Although the average decrease in IOP at 3 months follow-up was 1.09 mmHg, this reduction did not reach statistical significance (p-value = 0.06). The smallest reduction in this group was observed at the 1 month follow-up (0.98 mmHg) and the largest reduction was observed at 6 months follow-up (2.06 mmHg). The reduction in postoperative IOP was between 1.1 and 1.3 mmHg at all other follow-up time points (Table 2).

Amongst eyes that received FLACS, there was also a statistically significant decrease in IOP from preoperative to postoperative at 1, 6, 12, 24, and 36 months following surgery. While there was a decrease of 0.81 mmHg at month 3, this decrease was not statistically significant (p-value = 0.18). The largest reduction in postoperative IOP for this group was observed at 6 months follow-up (2.16 mmHg) and the smallest reduction was observed at the 3 months follow-up (0.81 mmHg) (Table 2).

Overall, compared to conventional phacoemulsification, eyes undergoing FLACS appeared to experience a generally larger reduction in IOP from preoperative to postoperative at all time points except for 3 months follow-up (Table 2). However, these differences between surgery types do not appear to be statistically significant.

Table 2, IOP change from baseline at each time point:

Month	IOP Change with Conventional PE N	Mean	95% CI	p-value [1]	IOP Change with FLACS N	Mean	95% CI	p-value [1]
1	67	-0.98	(-1.71 , -0.25)	0.009*	43	-1.14	(-1.88 , -0.41)	0.003*
3	39	-1.09	(-2.21 , 0.04)	0.06	27	-0.81	(-2.03 , 0.40)	0.18
6	33	-2.06	(-2.85 , -1.28)	0.0001*	24	-2.16	(-3.46 , -0.86)	0.002*
12	40	-1.26	(-2.24 , -0.28)	0.01*	26	-1.43	(-2.50 , -0.36)	0.01*
24	79	-1.10	(-1.73 , -0.47)	0.0009*	56	-1.51	(-2.33 , -0.67)	0.0006*
36	40	-1.18	(-1.93 , -0.42)	0.003*	26	-1.42	(-2.29, -0.54)	0.003*

[1] p-value from a paired t-test comparing postoperative IOP to average preoperative IOP for each treatment at each time point

*Statistically significant result at $p < 0.05$

Postoperative IOP among those who received FLACS was lower compared to those who received conventional phacoemulsification at 1, 3, 12, and 36 months follow-up points. However, this difference was not statistically significant at any of these time points (Table 3).

Table 3, Comparison of mean postoperative IOP at each time point:

Month	Postoperative IOP among Conventional PE			Postoperative IOP among FLACS			p-value [1]
	N	**Mean**	**95% CI**	**N**	**Mean**	**95% CI**	
1	67	15.6	(14.9 , 16.3)	43	15.3	(14.5 , 16.1)	0.62
3	39	15.6	(14.8 , 16.4)	27	15.4	(14.2 , 16.7)	0.87
6	33	14.2	(13.2 , 15.3)	24	14.8	(13.7 , 15.8)	0.50
12	40	15.6	(14.5 , 16.8)	26	14.9	(14.1 , 15.7)	0.31
24	79	14.7	(14.1 , 15.2)	56	14.9	(14.1 , 15.6)	0.67
36	40	15.0	(14.2 , 15.8)	26	14.4	(13.6 , 15.2)	0.28

[1] p-value from an unpaired t-test comparing postoperative IOP between conventional phacoemulsification vs. FLACS
*Statistically significant result at $p < 0.05$

The results from the final linear regression model with last measured postoperative IOP as the outcome and surgery type as the exposure are presented in Table 4. This final model accounted for preoperative IOP and race since they both exhibited a significant association with the outcome (p-value < 0.1). All other variables including age, gender, eye side, eye sequence, and surgeon were eliminated as they did not exhibit any significant association (p-value > 0.1). The last IOP included in this analysis was the IOP at 36 months for 66 eyes (27.1%), IOP at 24 months for 109 eyes (44.7%), IOP at 12 months for 24 eyes (9.8%), IOP at 6 months for 17 eyes (7.0%), IOP at 3 months for 12 eyes (4.9%) and IOP at 1 month for 16 eyes (6.6%). Overall, the average length of follow-up among eyes was 22.3 months.

After accounting for preoperative IOP, month to follow-up and race (effect modifier), postoperative IOP was lower in eyes undergoing FLACS compared to those who received conventional phacoemulsification across all racial groups (Table 4). Amongst Caucasian patients, postoperative IOP was 0.17 mmHg lower in eyes undergoing FLACS compared to eyes undergoing conventional phacoemulsification. However, this decrease was not statistically significant (p-value = 0.55). Amongst African American patients, postoperative IOP was 1.90 mmHg lower in eyes undergoing FLACS compared to eyes undergoing conventional phacoemulsification. This difference reached statistical significance (p-value = 0.04). Amongst patients in the “others” racial category, the postoperative IOP was 3.38 mmHg lower in eyes undergoing FLACS compared to eyes undergoing conventional phacoemulsification. This difference was statistically significant as well (p-value = 0.009).

The linear regression model also showed for every 1 mmHg increase in preoperative IOP, there was a 0.44 mmHg increase in the postoperative IOP. This observation was very strong statistically (p-value < 0.0001). Finally, each additional month of follow-up did not lead to statistically significant changes in the postoperative IOP (p-value = 0.65).

Table 4, multivariable linear regression model with last postoperative IOP as outcome:

Variable	**ß coefficient (95% CI)**	**p-value**
Caucasian		
Conventional PE	[Reference]	
FLACS	-0.17 (-0.76, 0.41)	0.55
African American		
Conventional PE	[Reference]	
FLACS	-1.90 (-3.72, -0.08)	0.04*
Others		
Conventional PE	[Reference]	
FLACS	-3.38 (-5.92, -0.85)	0.009*
Preoperative IOP	0.44 (0.35, 0.54)	<0.0001*
Month to Follow-up	0.005 (-0.02, 0.03)	0.65

*Statistically significant result at p < 0.05

From the sensitivity analysis, which included the second eye undergoing cataract surgery amongst all those who had surgery on both eyes, we found similar results to those presented in Table 4 (Appendix 2). The only notable difference was the result for African Americans where the postoperative IOP of those receiving FLACS was similar to that found in the previous analysis at 1.83 mmHg lower compared to conventional phacoemulsification. However, this reduction was not statistically significant (p-value = 0.05).

CHAPTER 4

Discussion

The main goal of this study was to compare the long-term postoperative IOP lowering effect of FLACS to conventional phacoemulsification. Before the beginning of this study, we hypothesized that eyes undergoing conventional phacoemulsification would have a lower postoperative IOP compared to those undergoing FLACS. We formed this hypothesis based on two factors:

1. A strong body of evidence suggesting FLACS uses less ultrasound energy as compared to conventional phacoemulsification[10,11,12]
2. Multiple previous hypotheses indicating ultrasound energy is the main reason behind the IOP lowering effect observed[18,21,22,23].

Our final findings, however, provided evidence against our initial hypothesis.

The most important finding of our study is that among non-Caucasian patients, FLACS led to a significantly larger postoperative IOP reduction compared to conventional phacoemulsification. In African American patients, after accounting for preoperative IOP and length of follow-up, postoperative IOP was 1.9 mmHg lower in eyes that received FLACS. This difference was statistically significant over 22 months of follow-up (p-value = 0.04). More importantly, this difference is considered clinically significant. According to Early Manifest Glaucoma Trial (EMGT), every 1 mmHg decrease in IOP is associated with 10% decreased risk of glaucoma progression[47]. Therefore, it can be inferred that in African American patients, FLACS could reduce the risk of glaucoma progression by 19% compared to conventional phacoemulsification. This is also clinically important since glaucoma tends to be more aggressive in African Americans[48] and these patients could benefit from any intervention reducing the risk of glaucoma progression. Among patients who did not come from African American or Caucasian ancestry, after accounting for preoperative IOP and the length of follow-up, postoperative IOP was 3.38 mmHg lower in eyes that received FLACS. This difference was statistically significant over the same length of follow-up (p-value = 0.009). However, what makes these findings valuable is their clinical significance. According to the association identified by the EMGT[47], these results indicate that in patients who did not come from African American or Caucasian ancestry, FLACS could reduce the risk of glaucoma progression by over 30% compared to conventional phacoemulsification. Finally, among Caucasian patients, there was no statistically or clinically significant difference in postoperative IOP between eyes that underwent FLACS versus conventional phacoemulsification.

Amongst all eyes undergoing FLACS, we observed an average of 1.43 ± 2.66 mmHg, 1.51 ± 3.10 mmHg and 1.42 ± 2.16 mmHg crude decrease in postoperative IOP from baseline over 1, 2 and 3 years of follow-up respectively (p-values = 0.01, 0.0006 and 0.003 respectively). As shown, reduction in postoperative IOP was more than 1 mmHg at all three follow-up points. Therefore, FLACS leads to a clinically significant reduction in postoperative IOP at all of these time points. This crude reduction, however, was much larger than what was reported previously by Shah at al. in 2019[41]. In eyes without glaucoma, Shah et al. reported a mean reduction of 0.27 mmHg in postoperative IOP at 2 years and a mean 0.08 mmHg increase in postoperative IOP at 3 years follow-up (p-value

= 0.24 and 0.82 respectively)[41]. Moreover, the difference they found was neither statistically nor clinically significant[41]. One explanation for the difference between our findings and those of Shah et al. is that they calculated these changes in IOP using a linear regression model (adjusting for age, sex, and preoperative IOP) while we obtained our results using a paired t-test looking at the crude change in postoperative IOP from baseline. The t-test is unable to account for confounders, and therefore it presents a potentially biased estimate. The other reason behind the difference is unequal sample sizes between our study and previous literature. For instance, in our study, only 56 eyes in the FLACS group had 2 years follow-up IOP and only 26 had 3 years follow-up IOP measurements. These numbers were 88 eyes and 52 eyes, respectively, in the Shah et al. study[41]. It is possible that smaller sample size in our study has led to a more exaggerated measure of the reduction in IOP from baseline.

Amongst all eyes undergoing conventional phacoemulsification, we observed an average of 1.26 ± 3.07 mmHg, 1.10 ± 2.84 mmHg and 1.18 ± 2.37 mmHg decrease in postoperative IOP from baseline over 1, 2 and 3 years of follow-up respectively (p-values= 0.01, 0.0009 and 0.003 respectively). These results indicate that conventional phacoemulsification leads to a clinically and statistically significant reduction in postoperative IOP at 1, 2, and 3 year time points. Additionally, the magnitude of reduction in IOP was comparable to what has been previously reported in the literature[22,37]. In the Poley et al. study, eyes that had a preoperative IOP of 15-17 mmHg (similar to the preoperative IOP of eyes in our study) experienced an average of 1.4 ± 2.4 mmHg reduction in their IOP postoperatively at 1 year[37]. Our findings were also comparable to the Damji et al. findings where postoperative IOP reduction (compared to baseline) in healthy eyes over 1 and 2 year follow-up was 0.84 ± 0.42 mmHg and 0.62 ± 0.42 mmHg respectively[38].

Overall, our findings in this project are novel in two regards. Frist, it was previously established that FLACS uses less ultrasound energy compared to conventional phacoemulsification[10,11,12]. Therefore, given that the preoperative IOP was similar between the two treatment arms, we expected to see a lower postoperative IOP in eyes undergoing conventional phacoemulsification. However, our results were exactly the opposite of what we expected. These findings challenge previous hypotheses about the role of ultrasound energy in IOP reduction. Currently, one of the main hypotheses is the belief that ultrasound energy remodels trabecular meshwork, improves aqueous outflow, and lowers the IOP postoperatively[21,18,23]. If this was the only mechanism responsible for IOP reduction, larger ultrasound energy used during the conventional phacoemulsification should have led to a lower postoperative IOP in eyes that received this treatment. However, our results suggest that increased ultrasound energy leads to a smaller decrease in postoperative IOP in eyes that did not belong to Caucasian patients. Therefore, based on our findings, we propose a new mechanism. We hypothesize that ultrasound energy only results in constructive remodeling of trabecular meshwork before a certain threshold. If the overall energy used during the surgery is below this threshold, aqueous humor outflow is improved, resulting in a significantly decreased IOP postoperatively. However, once the ultrasound energy surpasses this hypothetical threshold, we observe destructive effects on trabecular meshwork leading to less efficient outflow and smaller IOP reduction postoperatively. Our new hypothesis could explain why in non-Caucasian patients, eyes undergoing FLACS showed lower postoperative IOP compared to eyes undergoing phacoemulsification. Perhaps in these eyes, the ultrasound energy used during the surgery was below the hypothetical threshold. As a result, trabecular meshwork was remodeled very efficiently leading to improved outflow and lower postoperative IOP.

Secondly, our findings are novel as they suggest race modifies the relationship between postoperative IOP and surgery type (FLACS as compared to conventional phacoemulsification). To our knowledge, no previous study directly investigated effect modification by race. This effect modification by race could be explained by the presence of known differences in anterior chamber anatomy between different racial groups[35,34]. A recent cross-sectional study in the University of California, San Francisco (UCSF) showed that compared to Caucasians, Hispanics have the smallest lens position (LP) and relative lens position (RLP)[34]. This study defined LP as anterior chamber depth + half of the lens thickness and RLP was defined as LP divided by the axial length of the eye[34]. This study also showed that both measurements in Asian patients were the second lowest among racial groups compared[34]. The author concluded that the smaller LP and RLP in Hispanics and Asians suggest these patients have a much narrower angle compared to Caucasians[34]. A separate study by Oh et al. showed that iris root inserts more anteriorly in Asians, followed by African Americans translating into a narrower angle in these patients[35]. This connection point was noted to be the most posterior in Caucasian patients[35]. Finally, in 2013 Lee et al. conducted a prospective study at UCSF comparing six different iris thickness parameters between different racial groups[49]. Their results showed that in open-angle patients, the mean value for all six iris thickness measurements was higher in Chinese-Americans compared to all other races[49]. On the other hand, in the narrow-angle population, African Americans had the highest mean iris thickness measurements in 5 out of 6 categories[49]. A combination of these studies suggests African Americans have a narrower angle compared to Caucasians, while Asians and Hispanics have the narrowest angle amongst all other racial groups[34,35].

Combining this knowledge of known ocular difference with our new hypothesis about the ultrasound energy threshold, we can explain the effect modification by race seen in our study. In Caucasians, who have the widest angle compared to other races[34], aqueous humor has an easily accessible path. Therefore, even when the trabecular meshwork is damaged, due to the extra ultrasound energy used during the surgery, the total outflow of aqueous humor won't be heavily affected. As a result, there is essentially no difference between the IOP lowering of FLACS versus conventional phacoemulsification in these patients. On the contrary, African American patients with significantly narrower angle compared to Caucasians[34], heavily rely on the trabecular meshwork patency to drain aqueous humor. Therefore, the damage on the trabecular meshwork through the extra ultrasound energy, however small it may be, makes it more difficult for aqueous humor to drain. As a result, the IOP lowering effect of FLACS compared to conventional phacoemulsification is more pronounced in these patients. Finally, Hispanic and Asian patients who have the narrowest angles amongst all racial groups[34], are the most sensitive to the patency of trabecular meshwork. Therefore, these patients exhibit the biggest difference between the IOP lowering of FLACS versus conventional phacoemulsification. In our study, patients in the “Others” racial group came from a broad range of races. Amongst these are Asian and Hispanic patients which could explain the effect modification of this race category observed in our data.

The connection between angle anatomy and IOP reduction after cataract surgery was previously speculated by Shrivastava and Singh[17]. These authors conducted a literature review and concluded that angle anatomy might have an influence on the IOP lowering effect observed after the cataract surgery[17]. They especially emphasized that eyes with narrower angles are expected to experience a bigger reduction in postoperative IOP compared to eyes with normal angle width[17].

Strengths & Limitations

Strengths:

Our study has several major strengths. First and foremost, this is the first longitudinal study directly comparing the IOP lowering effect of conventional phacoemulsification to FLACS over a 3-year follow-up period. Even though there are plenty of data regarding various clinical outcomes of FLACS[9,10,40], the IOP lowering effect of this technology has only been investigated by one prior study[41]. Our study for the first time addressed this gap in knowledge and directly compared postoperative IOP in eyes that received FLACS to eyes that received conventional phacoemulsification.

We also took several steps in the study design and data collection process to minimize potential sources of bias/error and increase the internal validity of the study. In the design stage, we excluded all patients with the diagnosis of glaucoma, atypical ocular anatomy or history of IOP lowering medication use from the study. Doing so ensured that the observed changes in postoperative IOP were primarily caused by cataract surgery, not other factors. Similarly, we excluded any patients with a history of vitrectomy or retinal repair since these procedures are associated with an increase in postoperative IOP[43,44].

Furthermore, given that the treatment in this study is not randomized, we recognized there was a potential for bias through confounding by indication. The decision to pursue one surgery type over another is made based on the presence of certain contraindications[30] as well as the patient's ability to pay for the extra cost of FLACS. To address this source of bias, we eliminated all glaucomatous eyes from our study. Given that severe glaucoma is one of the main contraindications to FLACS[30], eliminating patients with glaucoma helped us address some of the confounding by indication. We subsequently compared the distribution of surgery type between surgeons to detect any fundamental differences between surgeon preference for one surgery. Our analysis showed no statistically significant difference in the distribution of surgery type between surgeons (p-value = 0.70). These findings suggest that surgeons participating in this study were equally likely to use one surgery type versus another. Both of these steps helped us minimize confounding by indication. However, we acknowledge there will be some residual unmeasurable confounding by indication in this study.

Additionally, our study included surgeries performed by three experienced surgeons. Having multiple surgeons in the study ensured that the observed difference between the two surgery types was not due to a specific technique used by a single provider. Having multiple surgeons also effectively increases the generalizability of our findings.

Finally, we prioritized Goldmann applanation tonometer (GAT) measurements for both preoperative and postoperative IOPs. There are several acceptable methods of measuring IOP in the clinic, including ocular blood flow tonograph (OBF), non-contact tonometers (NCT), Tono-Pen and GAT[50]. While some of these automated methods have their own advantages, GAT remains the gold standard for measuring IOP[50]. In fact, a study by Tonnu et al. in 2005 showed that repeated readings obtained from GAT are significantly more reproducible than other forms of IOP measurement[50]. To ensure the highest quality IOP measurements, we prioritized IOP obtained via GAT in this study.

Our choice of statistical analysis was also a major strength of this study. We used a linear regression model to compare the long term IOP lowering effect of two surgical types. This model allowed us to account for preoperative IOP and length of follow-up while investigating other potential confounders. Many previous studies used t-test to compare the change in postoperative IOP. While the t-test is an appropriate analytical method, it is unable to account for potential confounders and effect modifiers. Therefore, the effect observed obtained from t-test has the potential to be biased.

Limitations:

There are also several limitations to our study. As with all retrospective studies, one of the main limitations of this project was several missing data points. We tried to overcome this shortcoming using a linear regression model with the last available postoperative IOP as our primary outcome.

Another limitation of our study is the selection bias involved in the study design. All the data included in our project came from a single ambulatory surgical center. Recruiting patients from a single surgical center with a primarily Caucasian patient population can potentially limit the generalizability of our findings.

Given that this was a retrospective study, the accuracy and precision of our data, especially IOP measurement, is another limitation. Since we could not limit the number of individuals responsible for measuring IOP or train them before the study initiation, we do not know if people making the study measurements followed the same technique and made accurate measurements. Therefore, there may have been some random error in measuring preoperative and postoperative IOP. Luckily, this source of random error is non-differential and if present, it should push the results toward the null.

Finally, although we tried to collect information on all known confounders and account for the significant ones in our statistical analyses, it is possible that there is some residual confounding introducing bias into our study.

Clinical Implications

The main implication of this project is to help surgeons with critical preoperative decision making. According to the latest data from the World Health Organization (WHO), cataract and glaucoma are two of the top leading causes of blindness worldwide and they often happen concurrently in patients[51]. Glaucoma is a disease characterized by the progressive loss of retinal ganglion cells in the optic nerve leading to a gradual loss of peripheral visual field[52]. The IOP remains the most easily modifiable risk factor for glaucoma[53]. Therefore, most of the available treatments for glaucoma focus on reducing IOP and slowing the progression of the disease[42]. Given that cataract surgery is safer than many other interventions used to treat glaucoma, it has been used in the past to lower postoperative IOP and treat glaucoma[54]. In fact, there is evidence indicating cataract surgery decreases dependence to the IOP lowering medication after the surgery and could be an acceptable long-term management for glaucoma, especially for patients who live in underserved areas with limited access to care[54].

FLACS is a significantly more expensive surgical method, and currently, it is believed to be superior to conventional phacoemulsification only in a small subset of patients[10,55,56]. Before completion of this project, there was only one study which investigated the IOP lowering effect of FLACS[41]. Therefore, when trying to choose the best cataract surgery method to achieve the lowest postoperative IOP, the choice between FLACS versus conventional phacoemulsification was not very clear. Our results show that, regarding long-term IOP lowering effects, FLACS is superior to conventional phacoemulsification in patients who are not from Caucasian ancestry. This is critical information for surgeons who intend to perform cataract surgery on their glaucoma patients with the goal of achieving the largest IOP reduction post-surgery. In fact, it can be inferred that in Caucasian patients, where the two surgeries are equal with respect to their IOP lowering effect, patients should undergo conventional phacoemulsification which is the more affordable option. On the other hand, in African Americans patients who tend to have a more aggressive glaucoma[48], FLACS might be a better surgical option as it leads to a significantly lower postoperative IOP compared to conventional phacoemulsification.

Future Direction

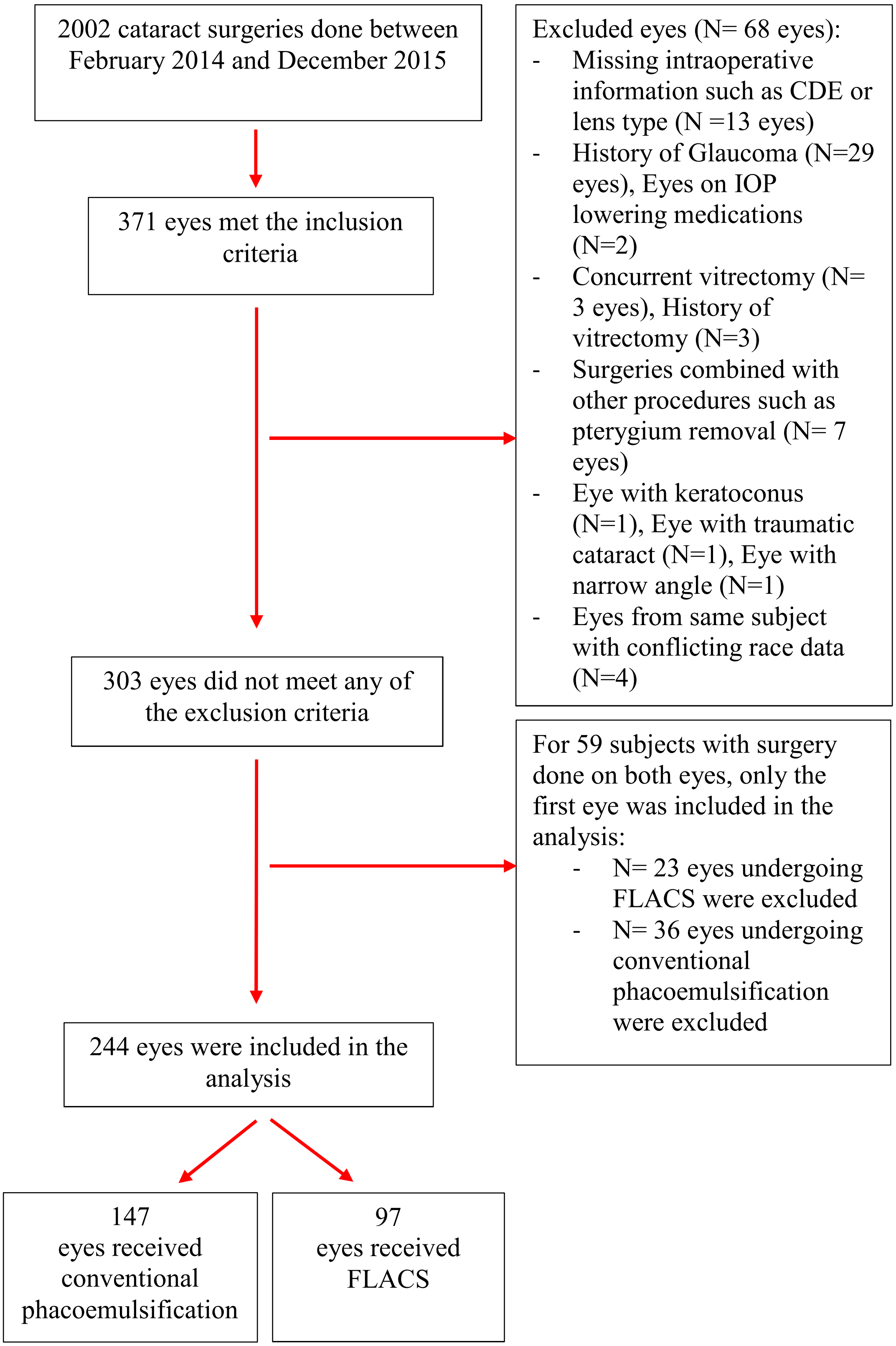
To our knowledge, this project is the second study investigating the IOP lowering effect of FLACS. While both our study and the work by Shah el al.[41] are retrospective cohort studies, they are very different with respect to the target populations, sample size, analytical approach and follow-up period. Therefore, more studies in the future are needed to truly establish the IOP lowering effect of FLACS as compared to conventional phacoemulsification.

For future work, we suggest a prospective multi-center cohort study with 3-5 years of postoperative follow-up to further characterize the IOP lowering effect of FLACS. This proposed project can overcome the limitations of our study by using the average of two consecutive GAT IOP measurements at each study visit, limiting the individuals making study related IOP measurement to 1-2 technicians/residents per study site, training the individual obtaining study measurements prior to the study, recruiting patients from multiple surgical centers, reducing the missing follow-up points by providing patients with incentives, collecting detailed information on the racial background of patients, collecting information on the cataract grade as well as the cumulative dissipated energy (CDE), and collecting detailed information on anterior chamber depth, lens thickness and axial length to calculate LP and RLP for each individual. Using the average of two consecutive GAT measurements as opposed to one ensures data precision and limiting the number of people responsible for obtaining IOP measurements and training them prior to the beginning of the study ensures data accuracy. Detailed racial classification and anterior chamber measurements allow for further testing of the effect modification by race observed in our study. Comparing the two cohorts with respect to cataract grade would ensure that the observed difference in IOP lowering effect was not derived from significant difference in cataract density. Finally, analyzing the CDE data would confirm that FLACS indeed leads to lower ultrasound energy compared to conventional phacoemulsification. Additionally, CDE data can be compared between racial categories to ensure that the observed effect modification by race was not derived from fundamental difference in ultrasound energy between the races.

Conclusion

Femtosecond laser assisted cataract surgery (FLACS) leads to a significant reduction in postoperative IOP compared to baseline both immediately after surgery (at 1 month follow-up) and over long term follow-up (2-3 years postoperatively). In non-Caucasian patients who were followed for an average of 22 months, the postoperative IOP was significantly lower in eyes that underwent FLACS compared to eyes that underwent conventional phacoemulsification after controlling for the preoperative IOP and length of follow-up.

Appendix 1: Flow diagram demonstrating data cleaning process:



Appendix 2: multivariable linear regression model with last postoperative IOP as outcome when analyzing the second eye undergoing cataract (sensitivity analysis):

Variable	ß coefficient (95% CI)	p-value
Caucasian		
Conventional PE	[Reference]	
FLACS	-0.10 (-0.69, 0.48)	0.73
African American		
Conventional PE	[Reference]	
FLACS	-1.83 (-3.66, 0.002)	0.05
Others		
Conventional PE	[Reference]	
FLACS	-3.26 (-5.80, -0.71)	0.01*
Preoperative IOP	0.47 (0.37, 0.57)	<0.0001*
Month to Follow-up	0.004 (-0.02, 0.03)	0.76

*Statistically significant result at p-value < 0.05

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