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RESEARCH ARTICLE

Femtosecond Laser Applications in Ophthalmic Surgery

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ABSTRACT:
Femtosecond laser's ultra-fast pulse duration results in a precise cut with low thermal energy. This precise and directed energy with low collateral tissue damage has been shown to be advantageous for ocular surgery with proven safety and reproducibility. The history and science, of femtosecond lasers as well as their evolution in eye surgery is discussed. The practical and current use of femtosecond laser in eye surgery is presented including its application in laser assisted cataract surgery, laser assisted ketatomileusis flap creation, intracorneal ring segment placement, femtosecond lenticle extraction, small incision lenticle extraction, creation of tunnels for presbyopic correcting corneal inlays, and femtosecond laser assisted penetrating keratoplasty. In each of these applications, the benefits and risks of the femtosecond laser procedure are reviewed and potential future applications of femtosecond in the field of Ophthalmic Surgery are discussed.

Introduction

The development of the Ruby Laser in 1960 by T.H. Maiman was quickly followed by an interest in ocular applications.[1] Transparent biological media, such as the refractive layers of the eye, can prevent the absorption of laser light. Linear absorption, however, occurs below a minimum wavelength. The advantage of such UV lasers (355 nm) is the small diameter of the beam, which can be focused down to a few micrometers. Still, linear absorption leads to deposition of laser energy and thermal damage throughout the beam path.[2,3] Nonlinear absorption occurs when the incident optical intensity is sufficient to stimulate the absorption of multiple photons, typically using pulsed lasers with pulse durations in the nanoseconds range.[4] While visible or near-infrared electromagnetic radiation alters the refractive layers of the eye at low power densities, short laser pulses at higher power densities in the near-infrared spectrum can stimulate nonlinear absorption that lead to plasma generation and tissue disruption.[5]

The first reported ophthalmic use of near-infrared lasers in clinical ophthalmology was in 1979 by Aron-Rosa who used a neodymium-doped yttrium aluminum garnet laser (Nd:YAG) to treat posterior capsule opacification following cataract surgery.[6] With a pulse duration in the nanosecond range and wavelength of 1064 nm, the Nd:YAG laser produces photodisruption at its focal point in tissue, resulting in a rapidly expanding cloud of free electrons and ionized molecules (plasma) and creating an acoustic shock wave that disrupts the treated tissue.[7] This process also leads to the formation of cavitation gas bubbles of carbon dioxide and water, which vaporizes small amounts of surrounding tissue. Nd:YAG photoionization, however, leads to collateral damage in surrounding tissue that exceeds 100 micrometers, rendering the Nd:YAG laser impractical for corneal surgery. The first study of femtosecond laser-tissue interactions in retinal tissue was published in 1987 and the first femtosecond assisted corneal surgery occurred in LASIK flap creation in the early 1990's.[8,9]

Femtosecond lasers operate in the infrared range of 1053 nm and use ultrafast pulses with a duration of 100 fs (10-15 seconds), which are not absorbed by optically clear tissues at low power densities.[10] Similar to the Nd:YAG laser, the femtosecond laser creates an incision by photodisruption at the laser's focal point. In femtosecond laser photodisruption, an ultra-fast pulse duration with high peak power is focused to a small area, causing a microburst of cavitation bubbles that create a cleavage plane, cutting tissue at very high precision inside the eye, essentially a "perfect cut," while also minimizing thermal damage to surrounding tissue. Shortening the pulse duration of the near-infrared laser from the nanosecond to the femtosecond range progressively reduces the magnitude of shock waves and the volume of cavitation bubbles, which in turn reduces the zone of collateral tissue damage to within 5 micrometers.[11,12] Furthermore, in cataract surgery, femtosecond laser systems can incorporate real-time imaging technology such as optical coherence tomography (OCT) or anterior segment imaging to provide high-resolution visualizations of the eye's structures which facilitate the creation of a consistently sized and precisely centered capsulotomy, treat corneal astigmatism, create clear corneal incisions, and cause fragmentation of lenticular material. In addition to applications in cataract surgery, there is a wide and evolving range of femtosecond laser advances in refractive surgery, most commonly in Laser Assisted In Situ Keratomileusis (LASIK) flap creation as well as in Small incision lenticule extraction (SMILE) and Penetrating Keratoplasty (PK). This review has the objective of identifying not only the application of femtosecond techniques, but to identify the risks, benefits, and potential advantages of this surgical modality. This is important to determine not only what gives the patient the most optimal results, but also delivering care in the most cost-effective manner.

Cataract Surgery

FEMTOSECOND LASER ASSISTED CATARACT SURGERY

Ophthalmic surgeons have been implementing lasers in cataract surgery for decades. Zoltan Nagy being the first to report the use of femtosecond lasers for cataract surgery. Since then, there has been rapid development of femtosecond technology and systems. In cataract surgery, the femtosecond laser can perform corneal incisions, capsular capsulotomies, lens fragmentation, arcuate incisions for astigmatism correction, and placement of corneal marks for alignment of toric IOL's. The first step of femtosecond laser-assisted cataract surgery (FLACS) is docking to the anterior surface of the eye to optimize visualizing ocular tissues and maintain centration and accuracy throughout the procedure. Recent developments in laser systems include iris registration for automatic cyclorotation compensation in astigmatism management.[13] Performing the capsulotomy with the femtosecond laser enables the surgeon to select the optimal diameter while maintaining precise centration. Studies have demonstrated femtosecond laser capsulotomies to be precise, predictable, repeatable, and perfectly centered as compared to manual continuous curvilinear capsulorhexis, resulting in better consistency of effective lens positioning.[13,14] Incomplete capsulotomies were observed in a minority of cases, manifesting in areas of uncut capsules, tags, and bridges, in which part of capsulotomy would need to be performed manually. In white, complete, or intumescent cataracts, studies have found that adjustment of femtosecond laser capsulotomy distance by reducing pre-anterior capsule and increasing post-anterior distance may decrease the incidence of incomplete capsulotomies.[16-18] The femtosecond laser allows nucleus fragmentation can be performed through various cutting patterns including cubes, sections, or grooves depending on surgeon preference and density of the cataract. As complications in cataract surgery including posterior capsule tear can frequently arise during nuclear disassembly, nuclear pre-cutting and nuclear softening with the femtosecond laser reduces the ultrasound energy required.[19,20] Studies have shown that reduction in the amount of ultrasound energy emitted from the phacoemulsification probe can diminish the risk of capsule complications and corneal endothelial cell injury.[21-23] Studies in porcine eyes have found femtosecond laser fragmentation resulted in a 43% reduction in phacoemulsification power required and a 51% decrease in phacoemulsification time. A comparative, retrospective study of FLACS versus conventional phacoemulsification (CP) carried out in a tertiary eye center including 2124 eyes found that FLACS resulted in a decrease in intraoperative complications.[16.] Other retrospective studies have found FLACS is comparable in safety to CP, if not safer, and had a lower overall complication rate compared to CP.[24,25] Despite aforementioned findings, a randomized multicenter clinical trial including 1476 eyes of 907 patients and meta-analysis studies could not prove the overall clinical advantage of FLACS versus CP.[12, 26.] It has been argued that FLACS is a useful tool in specific complex cataract surgeries.[27]

Several methods exist to correct astigmatism at the time of cataract surgery, the most common being implantation of a toric intraocular lens (TIOL) and corneal arcuate incisions that can be created manually or by femtosecond laser.[28,29] TIOL implantation is an effective and frequently used method for correction of higher astigmatism; however, disadvantages include the risk of misalignment, lens rotation, and surgically induced astigmatism.[30,31] Even mild degree of axis misalignment, especially in higher power TIOL's, can lead to a reduction in astigmatism correction.[32-34] Various conventional manual marking techniques have developed to minimize cyclotorsion and center TIOLs; however, image guided femtosecond laser systems are able to create corneal marks for placement of TIOL without manual preoperative manual marking. In 2010, Oscher reported a new method for improving accuracy in toric lens orientation through iris-fingerprinting, an iris registration system that uses the structures of the iris to perfectly identify the center of the eye and create reproducible, individually tailored, and precise corneal marks.[35] The application of corneal cuts to correct astigmatism was first reported in the nineteenth century; however, manual intrastromal arcuate keratotomy (ISAK) is associated with unpredictable results compared to TIOL implantation or corneal ablation.[36,37] Image-guided femtosecond laser technology based arcuate keratotomy procedures have been reported to improve the precision and predictability of incision parameters compared to manual limbal relaxation incisions.[38-41] A number of studies have evaluated the effectiveness and safety of femtosecond laser arcuate keratotomy in reducing pre-existing astigmatism in patients undergoing FLACS.[42-46] The femtosecond laser offers a new technology for the application of corneal cuts to address corneal astigmatism by delivering incisions with precision in position, length, depth, curvature, and keratotomy angle. These arcuate cuts can also be programmed to be entirely intrastromal which decreases postoperative discomfort and risks of infection. Additionally, new imaging platforms and preoperative planning algorithms allow for patient-specific preoperative planning and treatment, including iris registration and cyclorotation compensation, that improve safety and offer more accurate postoperative outcomes.[47] Indeed, studies have achieved a significant reduction in corneal astigmatism through customized calculation of corneal arcuate incisions based on individual corneal topography measurements and biomechanical simulations offering precise, patient-specific, and reproducible incisions, producing higher levels of patient satisfaction, and reducing overcorrection.[28, 48, 49]

Refractive Surgery

LASER ASSISTED IN SITU KERATOMILEUSIS FLAP CREATION

The argon fluoride (ArF) excimer laser which operates in the far-ultraviolet spectrum, was found to minimize thermal damage to surrounding tissue and maximize accuracy and precision of corneal ablation by an ablative photo-decomposition process. The excimer laser demonstrated more predictable outcomes than corneal reshaping achieved through manual radial keratectomy.[50] Photorefractive keratectomy (PRK) was the first refractive surgery approved by the FDA in 1996 involving excimer photoablation of the stroma after epithelial removal.[17, 51-53] Laser assisted in situ keratomileusis (LASIK) using a mechanical microkeratome to creates a lamellar corneal flap with subsequent excimer photoablation soon replaced most PRK procedures.[51]

By 2009, the femtosecond laser was used to create the corneal flap in 55% of all LASIK procedures performed in the US. The safety of femtosecond laser assisted flap creation has proved to be as effective as microkeratome-performed LASIK procedures.[54-56] With femtosecond laser flap creation, each pulse of the laser is applied to an adjacent focal point in the corneal tissue in the shape of a raster pattern, resulting in a cleave plane that creates a lamellar cut, followed by pulses applied in a peripheral circular pattern to create a vertical cut. In such a method, greater control of flap diameter, side-cut angle, hinge position and length which can lead to greater accuracy, predictability, and customization as compared with microkeratome flap creation. In addition, femtosecond laser-created corneal flaps present a more planar architecture opposed to microkeratome flaps, which often display a variability in thickness.[57] Multiple studies have demonstrated that femtosecond laser LASIK flaps yielded more predictable cuts, particularly in thinner flaps (100 to 110 micrometers).[58,59]

Femtosecond laser flap creation results in improved reproducibility of flap thickness, and improved safety through the creation of thinner flaps. A report of 196 myopic eyes found that thinner LASIK flaps are associated with faster visual recovery and with no difference in complication rates.[60] Femtosecond laser flaps displayed a standard deviation in flap thickness of 5 micrometers as compared to 20-40 micrometers with mechanical keratomes.[61-65] Thicker LASIK flaps can lead to lower residual stromal thickness with a corresponding higher risk of ectasia.[66]

Femtosecond laser flap creation significantly reduce the risk of flap complications such as buttonhole, free cap, and irregular cuts.[57] In addition, the femtosecond laser flaps demonstrate a stronger adherence, fewer induced higher order aberrations, better contrast sensitivity, less need for retreatment, lesser rate of epithelial ingrowth, and lesser incidence of post-procedure dryness.[67-71] Femtosecond LASIK flaps were first associated with complications derived from a stronger inflammatory response, such as diffuse lamellar keratitis and transient light-sensitivity syndrome, however, newer laser platforms with reduced energy delivery have demonstrated an overall inflammatory response not significantly different from the mechanical microkeratome.[57] Additionally, there is a benefit to femtosecond laser flaps in moderate to high hyperopia likely due to larger optical zones and thus larger peripheral ablations.[72]

Creating a flap with the femtosecond lasers leads to high levels of reproducibility and precision, however, it is not without the potential for complications.[73] The femtosecond laser creates microplasma that form an intrastromal cleavage plane by cavitation bubbles. Typically, cavitation bubbles collapse and dissipate during the flap lifting process. Some cavitation bubbles, however, are not expelled. One of the most common intraoperative complications of femtosecond laser-assisted LASIK involve accumulated cavitation bubbles.[73,74] In the presence of a corneal scar or abnormality in the Bowman's layer, gas dissects vertically toward the stroma or epithelium, following the path of least resistance. Vertical gas breakthrough is a rare but serious complication that results in an incomplete dissection of the flap with a potential for buttonholing, which can lead to corneal tearing, incomplete flaps, and even failure of the procedure.[75] Vertical gas bubbles have been observed in 0.03% to 0.13% of cases.[76,77] Cavitation bubbles may also form an opaque bubble layer (OBL) when a cavitation bubble is trapped within the corneal stroma.[71] OBLs are classified as early or late depending on whether they occur before or after the time of laser delivery. A persistent OBL can interfere with excimer laser delivery pupil tracking and potentially lead to an increase in higher order aberrations.[78-80] Thick cornea, small flap diameter, hard docking technique, corneal hysteresis, use of low laser frequency or energy, and small spot or line separation are risk factors associated OBL.[80] A method that promotes gas ventilation recently demonstrated a significant reduction in OBL incidence in a retrospective study of 1400 eyes of 715 patients receiving femtosecond-assisted LASIK surgery.[81] Other intraoperative complications of femtosecond flaps include suction loss, free cap, flap tear, buttonhole flap, decentered ablation, central island, and interface debris.[73] Postoperative complications include flap striae, flap dislocation, residual refractive error, diffuse lamellar keratitis, microbial keratitis, epithelial ingrowth, refractive regression, corneal ectasia, transient light sensitivity syndrome, and rainbow glare.[71,73]

INTRACORNEAL RING SEGMENT PLACEMENT

Keratoconus is a progressive corneal disease characterized by corneal steepening and thinning, generating myopia and irregular astigmatism.[82] Intracorneal ring segments (ICRS) are small polymethyl methacrylate devices that alter corneal topography and improve sphericity. Implantation of intrastromal corneal rings was first introduced by Colin in 2000 to treat keratoconus and post-LASIK corneal ectasias.[83-87] The procedure involves the insertion of ring segments into tunnels of corneal stroma created either mechanically or by use of a femtosecond laser at 75% depth of the thinnest pachymetry. The ICRS act as spacer elements between collagen fibers of corneal tissue that induce corneal flattening.[88] The effect of the procedure is proportional to the thickness of the implant and inversely proportional to the implant diameter. Manual tunnel creation can be associated with complications such as epithelial defects, anterior or posterior corneal perforation, infectious keratitis, asymmetric segment placement, corneal stromal edema around the incision, extension of the incision towards the central visual axis, or incisional gapping.[89-92]

Studies have demonstrated that creating a tunnel using the femtosecond laser is a safe and effective method.[93,94] In a retrospective chart review of 850 eyes of 531 patients who received a ICRS insertion using a femtosecond laser, Coskunseven reported an overall complication rate of 5.7% with the most common complications of incomplete channel creation (2.7%) and postoperative segment migration (1.3%).[89] Complications of mechanical intrastromal tunnel creation have been shown to be associated with higher rates as compared with femtosecond laser-assisted technique.[95]

FEMTOSECOND LENTICULE EXTRACTION AND SMALL INCISION LENTICLE EXTRACTION

Since the introduction of the femtosecond laser in 2007, there has been the ability to perform an intrastromal lenticule extraction procedure without using an excimer laser.[96] In 2008, Sekundo et al reported the 6-month results of the first 10 eyes treated with femtosecond lenticule extraction (FLEx).[97] In the FLEx procedure, the femtosecond laser not only creates the flap, but the corneal ablation, thus eliminating the need for excimer laser. The refractive results were similar to those observed in LASIK, but with longer visual recovery time. Further optimization of energy parameters and laser scanning technique led to improved visual recovery times,[98] and claims of less discomfort, decreased total procedure time, and better scotopic results. Following the successful implementation of FLEx, a novel procedure called small incision lenticule extraction (SMILE) was developed.

SMILE is a flapless femtosecond laser-assisted refractive procedure that eliminates the need for flap creation and thus flap-related potential complications. Studies have demonstrated that SMILE is associated with not only better biomechanical strength, but also a reduced incidence of dry eye.[17] The femtosecond laser delineates a refractive lenticule within the stroma, which is extracted through a 3.0 to 5.0 mm incision through the stroma without the need for flap creation or excimer photoablation.[66] The United States Food and Drug Administration (FDA) approved the procedure for spherical myopic corrections in 2016 and compound myopic astigmatism in October 2018.[99] Visual and refractive outcomes after SMILE have been demonstrated as similar to the outcomes achieved through LASIK.[96] In addition, further studies have shown the short-term and long-term safety, efficacy, and predictability of SMILE as a treatment for mild-to moderate myopia.[100] Because a small incision is used in place of a flap, corneal nerve severance is less as compared to LASIK, which is consistent with better recovery of corneal sensation and dry eye parameters observed in the SMILE procedure.[101-103] Additionally, SMILE has been demonstrated to produce less spherical aberration than femtosecond-assisted LASIK.[104,105] SMILE is also considered more cost effective to LASIK, because it requires one laser platform as compared to the two required by LASIK when a femtosecond laser flap is created and an excimer laser is used for tissue ablation.

SMILE is in its relative infancy as a refractive procedure but has already demonstrated similar visual outcomes and safety profile as compared with LASIK. There have been, however, concerns regarding the precision of astigmatism, specifically, a tendency towards under correction. Pedersen reported a 12 month under correction rate of approximately 11% (per diopter of attempted correction) in a study of 101 eyes.[106] Currently, there are no standardized nomograms for SMILE astigmatism correction.[107] Additionally, the learning curve of SMILE can be challenging with the lenticule dissection and extraction noted as the most difficult steps.[108] One current limitation of the technique is that there is no eye tracking device available with this procedure and axis errors due to cyclotorsion are more common. In addition, visual outcomes are often directly related to a surgeon's surgical skill and experience.[109] Li studied 100 eyes of 55 consecutive patients and found a mild horizontal decentration with an induced horizontal coma occurred more frequently in the early learning curve, but still resulted in good visual outcomes.[110] Chan demonstrated that faster visual recovery, better safety profile, and more accurate astigmatic correction could be attained with increasing surgical experience during the first two years of SMILE experience.[111] FLEx may also prove to be a therapeutic option for treatment of corneal ectasias, especially advanced keratoconus, by providing biomechanical support, and reducing corneal curvature.[31,112] Finally, SMILE extracted lenticules have been shown to successfully treat a recurrent pterygium complicated by a thin cornea.[113]

CORNEAL INLAY TUNNEL CREATION FOR PRESBYOPIA CORRECTION

Correcting presbyopia by surgical methods has been challenging and largely unsatisfactory for both the patient and surgeon. Refractive corneal inlays are disc shaped implants that use different circular refractive zones to modify the focal point and provide near vision similar to multifocal contact lenses or multifocal IOL's. Presently, no synthetic corneal inlays are available in the United States for the correction of presbyopia.[114.]

In investigation and FDA trials is the presbia flexivue micolens, a hydrogel implant with rings of progressively increasing power. It is 3 mm in diameter and placed at a depth of 3/5's corneal thickness. The Icolens System is a refractive hydrophilic polymer lens with no refractive power in the center and positive refractive power in the peripheral zone. Icolens is commercially available outside of the United States.[115] Corneal reshaping inlays to create a hyperprolate anterior corneal surface and reduce presbyopia are being investigated, including the Raindrop Near vision inlay. Finally, small aperture inlays create a pinhole effect to treat presbyopia (Kamra Inlay).

These corneal inlays can be implanted mechanically, however, creating a tunnel using a femtosecond laser can result in more reliable stromal pockets, which improves centration and greater accuracy of depth of placement.[116] Initial enthusiasm for corneal inlays has been dampened by concerns of complication including corneal haze as found with the Raindrop inlay. With the Kamra inlay, by 24 months, 3.4% of patients experienced a compromised visual acuity and 8.5% were removed due to corneal haze or cosmesis.[117,118] The Kamra inlay was discontinued in the United States in 2022.[119,120] The Raindrop inlay resulted in improved near and intermediate vision, but left some patients with corneal haze which did not resolve even after explantation, which led the FDA to recall the inlay in 2018.[119, 121, 122]

Penetrating Keratoplasty

FEMTOSECOND LASER ASSISTED PENETRATING KERATOPLASTY

Penetrating keratoplasty although successful, often is associated with a prolonged visual rehabilitation. Some advantages in healing have been accomplished with manual techniques using various shaped corneal grafts.[123] The femtosecond laser has been used to create reproducible dimensions in both donor and host tissues creating a better fit of the graft with the intent of decreasing postoperative astigmatism, enabling earlier suture

removal, and less incidence of wound leak and Descemet's folds.[124,125] By creating precise corneal incisions, the femtosecond laser can create customized grafts matched to recipient corneas, allowing for complex graft-host junctions and non circular graft designs.[73] Such customization has included Zig-Zig pattern, Christmas tree pattern, mushroom pattern (larger diameter anteriorly), and top-hat pattern (larger diameter posteriorly).[126,127] Studies have shown that femtosecond laser assisted keratoplasty (FLAK) improves the repeatability and consistency while enabling the surgeon to control the thickness and shape of the transplanted tissue.[128] Meta-analysis studies have shown visual outcome improvement for FLAK at 6 months but no better at 12 months.[129]

Conclusion

The Femtosecond laser with its ability to precisely cut tissue with low thermal energy and low collateral tissue damage. Such attributes have made the femtosecond a safe and reproducible method to perform eye surgery. As surgical procedures in general are becoming more robotic with a tendency toward microincision, less trauma, and quicker healing, so too are the trends in Ophthalmology. The femtosecond laser has been demonstrated to be useful in laser assisted cataract surgery to reduce astigmatism, lessen phacoemulsification total energy, and improve predictable and effective lens position. Studies are still investigating the cost effectiveness and overall advantages in patient's outcomes, but with improved iris registration and arcuate nomograms it is likely advantages will continue to be demonstrated. In lasik surgery, the femtosecond laser creation of corneal flaps has demonstrated improved precision, reproducibility, and fewer complications than mechanical keratomes. The femtosecond laser has shown great precision and accuracy in creating tunnels to place corneal rings and corneal inlays.

Small incision lenticule extraction has become an acceptable alternative to LASIK in certain cases due to the capabilities of delineation and extraction with the femtosecond laser. Finally, femtosecond laser assisted keratoplasty offers the promise of better and more secure graft fit with less postoperative astigmatism.

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