LOW INFLAMMATION IN NANOJOULE FEMTOSECOND LASER CATARACT SURGERY

Conclusions

1. Production of inflammatory mediators with the nanojoule FEMTO LDV Z8 is the lowest reported in the literature among all systems on the market.

2. No clinical evidence of significant pupil diameter changes with the FEMTO LDV Z8 was reported. The PG E2, involved in pupil constriction, showed the lowest values.

3. IL - 1 and IL - 6, responsible for the macular edema, PCO formation and pain, presented the lowest numbers with the FEMTO LDV Z8.

4. The central corneal thickness returns to pre-operative values at 1-week post-op. This ensures fast visual recovery when using the low energy laser.

5. Combination of mydriatic drops and NSAIDs is recommended to ensure sufficient mydriasis, as well as to suppress the production of inflammatory mediators.

Introduction

Peri- and post-operative inflammation and the intraocular effects, caused by surgical trauma, remain important issues in cataract surgery. A number of factors are known to be inducers of inflammatory responses, both in manual and femto-cataract surgery. Surgical trauma, ultrasound waves, intra-ocular manipulations, laser cavitation bubbles, and suction induce irritation of ciliary body. The ciliary body reacts by producing prostaglandins and other inflammatory mediators [1], [2].

Peri-operatively, the prostaglandins cause pupil miosis and lead to potential difficulties during the course of operation [1], [2]. Post-operatively, the inflammation causes pain [3] and slows down patients’ return to everyday activities. Anterior chamber flare and corneal swelling are known to influence visual recovery [4]. This becomes more important than ever before, as younger patients are now also undergoing cataract surgery for refractive reasons. With today’s fast paced lifestyle demands, younger people are eager to return to their workplaces without the hassle of taking pain medication or not being able to see well.

Due to its superior precision, refractive cataract patients mostly opt for femto-laser treatment [5], [6], [2]. The laser pre-fragmentation of a cataractous lens allows to use less ultrasound, needed for cataractous lens removal. In addition, the intra-ocular manipulations are reduced, thanks to both the laser lens fragmentation and laser capsulotomy. Thus, the effect of surgical trauma can be decreased.

Results

A number of recent articles described changes of concentrations of inflammatory mediators, such as prostaglandin and cytokines, in the anterior chamber after the phacoemulsification using different femto-laser systems [1], [7], [8], [9]. It appears that not all femto-second lasers are alike. The pulse energy plays a major role in the degree of inflammatory response. The lower pulse energy is most gentle towards the iris, ciliary body, and trabecular meshwork. It was also shown that FEMTO LDV Z8 nanojoule laser causes the minimum release of...
prostaglandin and cytokines compared to other devices on the market. The results are summarized in Table 1.

Schwarzenbacher, L. et al. [10] conducted a prospective randomized controlled study comparing the inflammatory impact of low pulse energy femto-second laser cataract surgery (FLACS) FLACS and conventional manual cataract surgery (MCS). The study was presented at ARVO Congress in 2018 with a title “Intraindividual comparison of proinflammatory cytokines (IL-1β, IL-6) and total-prostaglandin (PG) following Femtosecond Laser-assisted Cataract Surgery using a Low-energy, High-frequency Femtosecond Laser-Device compared to Manual Cataract Surgery.” Forty patients were included in the study and assigned to have either immediate sequential or same-day bilateral cataract surgery. The big value of this study is in its intra-individual comparison between FLACS and MCS design, avoiding all confounding effects related to differences in patient cohorts.

The authors found no changes of IL-1β and IL-6 concentrations 5 minutes after femtosecond laser treatment. Regarding total PG levels, an elevation to a mean concentration of 19.86 pg/mL in the femtosecond laser group compared with 15.6 pg/mL in the control eyes was detected, which is a 1.27-fold increase above the baseline. This is in striking contrast with reports using the Catalys laser, where the total PG increase was shown to be 175.7-fold [2]. The mean concentrations of 25.6 pg/mL IL-1β and 24.6 pg/mL IL-6 were found in aqueous humor after high pulse energy laser pretreatment with the Victus FSL system [12].

The findings regarding the IL-1β and IL-6 are in line with another report by Liu, Y.C. et al. [9] using FEMTO LDV Z8 entitled “Changes in aqueous oxidative stress, prostaglandins, and cytokines: Comparisons of low-energy femtosecond laser-assisted cataract surgery versus conventional phacoemulsification.” In a randomized controlled trial, the authors compared the oxidative stress, prostaglandin E2 (PG E2), and cytokine levels after low-energy FLACS versus conventional phacoemulsification. They also evaluated the effect of a nonsteroidal anti-inflammatory drug (NSAID) on the aqueous profiles. No significant differences in the levels of IL-1β and IL-6 between the two groups was found. Although total prostaglandin concentration was not examined in this study, the femtosecond-assisted group had a significantly higher level of PG E2 after laser pre-treatment compared with the conventional group (175.6 +/- 125.3 pg/ml versus 68.8 +/- 47.6 pg/ml, P = .01). In studies that used a high-energy (mJ) platform (Catalys or LenSx), the reported levels of PG E2 ranged from 182.1 pg/ml to 1911.4 pg/ml, [11], [13], [14], [15], which were higher than that reported in the present study when the low-energy (nJ) system was used (175.6 pg/ml).

When NSAID treatment was administered pre-operatively in femtosecond laser-assisted cataract surgery patients, the preoperative NSAID treatment significantly reduced the PG E2 levels to those seen in the conventional phacoemulsification group (175.6 +/- 125.3 pg/ml versus 63.4 +/- 35.9 pg/ml, P = .002). The values of inflammatory mediators described in these papers are summarized in the Figure 1 below.

![Figure 1. Values of IL-1β, IL-6, PG E2 and Total PG values in conventional cataract surgery, FEMTO LDV Z8 and other systems (pg/ml).](image-url)

Figure 1. Values of IL-1β, IL-6, PG E2 and Total PG values in conventional cataract surgery, FEMTO LDV Z8 and other systems (pg/ml). (FEMTO LDV Z8 values for IL-1β and IL-6 and PG E2 originate from Liu, Y.C. et al. [9], the Total PG from Schwarzenbacher, L. et al. [10]. Values for other systems were calculated out of values form several publications: [1], [11], [12], [13], [14], [15], and therefore more than one column for other systems is presented).

Another valuable finding of this research by Liu, Y.C. et al. [9] is the changes in aqueous Malondialdehyde (MDA) levels, which reflect the oxidative stress. Laser pre-treatment induced the generation of MDA, and the oxidative stress, induced during phacoemulsification, strongly correlated with effective phaco time (EPT), but not with the type of surgery.

Femtosecond laser-assisted cataract surgery requires adequate dilation for imaging and treatment. PG E2 is believed to be responsible for the miotic effect observed during the surgery [15]. Mirshahi A. et al. [18] detected no changes in the pupil area after comparing preoperative pupil status with post-laser size in their study entitled "Change in pupil area using a low-energy femtosecond laser in cataract surgery" using FEMTO LDV Z8. This is in contrast with studies using other laser platforms that assessed pupil changes in high-energy FLACS.

Diakonis et al. compared the effect of three different laser platforms (LenSx; Alcon Laboratories, Inc., Fort Worth, TX, Catalys; Abbott Medical Optics Inc., Santa Ana, CA, and Victus; Bausch & Lomb, Inc., Rochester, NY) on pupil diameter [19] and found a mean pupillary miosis of 1.42 ±1.26 mm for the LenSx, of 0.66 ±0.89 mm for the Catalys, and of 0.14 ±0.34 mm for the Victus groups. Approximately one-quarter of eyes included in this study demonstrated a pupil diameter of 6 mm or less. Jun et al. reported a 29.7% decrease in the pupil area after femtosecond laser pre-treatment in a study sample of 56 eyes using the Catalys [20].

These results are of clinical significance because small pupil size is generally considered to be a challenge, potentially leading to a higher incidence or severity of complications in cataract surgery [19].

The results, presented above, are summarised in Table 1. Inflammation mediators and inflammation indicators, their symptoms and values in conventional cataract surgery and with different femtosecond lasers.

<table>
<thead>
<tr>
<th>Mediator or inflammation indicator</th>
<th>Functions and symptoms when values decreased</th>
<th>Conventional</th>
<th>FEMTO LDV Z8</th>
<th>Other lasers</th>
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<tbody>
<tr>
<td><strong>IL - 1β</strong></td>
<td>Interleukin-1 receptor antagonist has been shown to suppress the proliferation of lens epithelial cells, [9] and this might provide a favorable view of femtosecond laser-assisted cataract surgery in the aspect of the occurrence of postoperative posterior capsular opacification. [9] Involved in the process of pathological pain. [21]</td>
<td>traces [10]</td>
<td>traces [10]</td>
<td>25.6 pg/ml [11]</td>
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<td></td>
<td></td>
<td>0.05 +/- 0.05 pg/ml [9]</td>
<td>0.5 +/- 0.2 pg/ml [9]</td>
<td>57.6 pg/ml [12]</td>
</tr>
<tr>
<td><strong>IL - 6</strong></td>
<td>Associated with cystoid macular edema after cataract surgery. [22] Involved in the process of pathological pain. [21]</td>
<td>0.48 pg/ml [10]</td>
<td>0.45 pg/ml [10]</td>
<td>24.6 pg/ml [11]</td>
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<tr>
<td></td>
<td></td>
<td>8.9 +/- 6.1 pg/ml [9]</td>
<td>7.3 +/- 6.9 pg/ml [9]</td>
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<tr>
<td><strong>Prostaglandin E2 (PG E2)</strong></td>
<td>This prostaglandin increase contributes to the miotic effect. [15]</td>
<td>68.8 +/- 47.6 pg/ml [9]</td>
<td>175.6 +/- 125.3 pg/ml [9]</td>
<td>182.1-1911.4 pg/ml [11], [13], [14], [15]</td>
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</table>
Results summary

Shockwaves, induced by femto-laser pulses, cavitation bubbles executing the resection, as well as the suction applied on the eye, are known to stimulate the ciliary body to release inflammatory mediators into the anterior chamber [2]. High pulse energies create shock waves and large cavitation bubbles that induce stress to the surrounding tissue, whereas low pulse energies create smaller bubbles and smaller cavitation bubbles, that impose less of a stress effect. FEMTO LDV Z8 is the only femtosecond laser that uses very low energy, working in the nanojoule and megahertz range, ensuring not only smooth and gentle resections but also minimal collateral damage compared to other systems.

Previously, it has been shown in both cornea and cataract surgeries, that the collateral damage, namely the healing response and the cell death, decreased together with the decrease of applied energy [23], [24], [25]. We presented results that corroborate these reports and indicate, that the inevitable for every surgery inflammatory response is pronounced the least with the low pulse energy FEMTO LDV Z8.

In contrast to other systems, the total prostaglandin, responsible for the intra-operative miosis, was found to increase only slightly when the FEMTO LDV Z8 was used [10]. This laboratory finding was confirmed by the clinical observations of Mirshahi A., et al. [18] who reported no changes in the pupil area when preoperative pupil status was compared with its post-laser size. Low energy laser will, therefore, provide the best conditions for maintaining constant pupil diameter throughout the surgery and will avoid peri-operative myosis-related complications.

In addition, due to its mobility and versatility, when using the FEMTO LDV Z8, the surgery can be continued immediately after the completion of laser pre-treatment, whilst when using other lasers, patients must be transferred to another surgical table or theater in order to continue the surgery. The extended time lapse between laser pre-treatment and further surgical steps may be an additional factor for much higher incidences of intraoperative miosis in these cases [13], [2], [19].

One important recommendation comes from the research of Liu Y.C., et al. The authors found, that the preoperative NSAID treatment significantly reduced the PG E2 levels to those seen in the conventional phacoemulsification group. A number of different NSAIDs administration regimes are described in the literature [26], [27] and it is a common practice to add the NSAIDs to the mydriatic drops in order to maintain large pupil throughout the surgery.

Posterior Capsular Opacification (PCO) is the most common complication associated with cataract surgery. It results in the need for millions of posterior capsulotomies via Nd:YAG lasers each year. The IL - 1β, hypothesized to be involved in postoperative PCO [9], was found at its lowest level when FEMTO LDV Z8 was used. Thus, a patient undergoing FLACS with the low energy laser might have a potentially lower risk of PCO formation.

A number of contradictory reports on the post FLACS macular thickness have appeared in recent years where some authors found no differences in macular thickness between FLACS and conventional groups [29], [30], while others indeed found some dissimilarities [31]. The
differences in these reports might have been related to different laser energies used in these studies that require further investigation. The IL - 6, associated with cystoid macular edema after cataract surgery [22], showed the lowest concentrations after using FEMTO LDV Z8 compared to other systems.

As reported by Mariacher S., et al. when using FEMTO LDV Z8, the median CCT returned to preoperative values as soon as one week after surgery. It will undoubtedly contribute to fast visual recovery and patients’ satisfaction.

Another important finding also highlighting general advantages of FLACS in cataract surgery is that the oxidative stress, induced during phacoemulsification, strongly correlates with effective phaco time (EPT), but not with the type of surgery. The EPT after femtosecond laser pre-treatment of the lens is reported to be significantly shorter than with conventional cataract surgery [28]. Therefore, the femto-second lens fragmentation could potentially lead to reduced oxidative stress.

Conclusions

1. Production of inflammatory mediators with the nanojoule FEMTO LDV Z8 is the lowest reported in the literature among all systems on the market.

2. No clinical evidence of significant pupil diameter changes with the FEMTO LDV Z8 was reported. The PG E2, involved in pupil constriction, showed the lowest values.

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4. The central corneal thickness returns to pre-operative values at 1-week post-op. This ensures fast visual recovery when using the low energy laser.

5. Combination of mydriatic drops and NSAIDs is recommended to ensure sufficient mydriasis, as well as to suppress the production of inflammatory mediators.

6. The oxidative stress, induced during phacoemulsification, does not depend on the type of surgery (manual or FLACS), but strongly correlates with effective phaco time (EPT). FLACS provides an important advantage in this case by decreasing the EPT.
References

10. Luca Schwarzenbacher, M.D.S., MD, Willi Mühlbacher, MD, Marion Funk, MD, Christina Leydolt, MD, Rupert Menapace, MD, “Intra-individual comparison of cystoid and prostaglandin levels in low pulse energy, high-frequency femtosecond laser-assisted and manual cataract surgery”. Presented at ARVO, Honolulu. Submitted for publication.