Acta Ophthalmologica

Ultrasound energy consumption and macular changes with manual and femtolaser-assisted high-fluidics cataract surgery: a prospective randomized comparison

Rupert Menapace,[1] Daniel Schartmüller,[1] Veronika Röggla,[1] Gregor S. Reiter,[1,2] Christina Leydolt[1] and Luca Schwarzenbacher[1]

[1]Department of Ophthalmology, Medical University of Vienna, Vienna, Austria
[2]Christian Doppler Laboratory for Ophthalmic Image Analysis, Department of Ophthalmology and Optometry, Medical University of Vienna, Vienna, Austria

ABSTRACT.
Purpose: **The purpose of the study was to compare ultrasound (US) consumption and central macular thickness (CMT) and volume changes with manual and femtosecond laser (FSL)-assisted cataract nucleus workup.**
Methods: **Sixty patients scheduled for immediate sequential bilateral surgery underwent a prospective randomized intraindividual comparison of nucleus sector fragmentation performed manually in one eye and with low-energy FSL assistance in the partner eye, followed by high-fluidics phacoaspiration with a maximum US power of 30%. Ultrasound (US) energy consumption and macular thickness and volume were compared as measured by intraoperative effective phacoemulsification time (EPT) and high-resolution spectral domain optical coherence tomography pre- and 1 week, 3 weeks and 6 weeks postoperatively. Results are presented as means ± SD or medians [min; max].**
Results: **Fifty-two patients completed the full follow-up. For the manual and FSL-assisted groups, nuclear hardness was almost identical with a mean LOCS III grade of 2.44 ± 1.08 and 2.50 ± 1.00 (p = 0.371). Median EPT was 1.40 [0.2; 8.3] and 1.25 [0.2; 9.4] seconds. Median preoperative CMT was 276.50 [263.25; 289.75] µm and 276.00 [262.00; 290.00] µm. Median postoperative CMT was 278.00 [260.50; 288.00] versus 275.50 [264.00; 290.50] µm at 1 week, 279.50 [266.75; 292.25] versus 280.00 [266.50; 294.50] µm at 3 weeks and 280.50 [268.00, 293.75] versus 279.50 [264.75; 295.25] µm at 6 weeks. Differences in CMT and total macular volume between the groups were not statistically significant at any point in time.**
Conclusion: **Femtosecond laser (FSL) prefragmentation of the nucleus into six sectors did not reduce US energy consumption compared with manual splitting of the nucleus into four quadrants in this particular surgical setting. Sectorial FSL-prechopping with the low-energy FSL used had no additional impact on postoperative macular thickness and volume.**

Key words: central macular thickness – femtosecond laser-assisted cataract surgery – high-fluidics phacoemulsification – low-energy femtosecond laser – total macular volume – ultrasound energy consumption

Acta Ophthalmol. 2022: 100: e414–e422

doi: 10.1111/aos.14983

Introduction

Since its introduction in 1968, phacoemulsification (phaco) has quickly spread to become the dominating technology for cataract removal. By refining nucleus division techniques and fully exploiting the potential of fluidics and ultrasound (US) modulation, US energy consumption has been largely reduced over time. Today, phaco chop and torsional or longitudinal high-fluidics phaco are considered state of the art providing optimum efficiency and safety (Storr-Paulsen et al. 2008; Menapace & Di Nardo 2010; Vasavada et al. 2010).

Femtosecond lasers (FSLs) have been introduced in cataract surgery to achieve a perfectly shaped and centred anterior capsular opening and to make nucleus workup easier and reduce the consumption of potentially hazardous US energy. Effective phaco time (EPT) is the most common measure for US energy consumption. Laser cataract surgery (LCS) with FSLs has been shown to potentially reduce EPT for nuclear workup compared with manual cataract surgery (MCS) alone, with the amount of savings depending on the fragmentation pattern (Conrad-Hengerer et al. 2012; Abell et al. 2013a,b; Dick & Schultz 2017; Uy et al. 2019). However, EPT is the mere product of US time and US power. High US power released in a short time and low US power released over a longer time period resulting in the same EPT may have a significantly different damage potential to intraocular tissues.

A phacoemulsification tip oscillating at US frequencies generates cavitation bubbles through the phenomenon of sonolysis, which directly causes disintegration of water molecules and formation of hydroxyl radicals. Free radical dispersion increases in proportion to the amount and duration of the US power used (Cameron et al. 2001; Gardner & Aust 2009). Free hydroxyl radicals are among the most reactive of all oxygen species and may provoke endothelial cell damage, blood–aqueous barrier (BAB) failure and changes in macular thickness, volume and structure, which may ultimately result in cystoid macular oedema (CME) (Takahashi 2005). The actual damage potential depends on the total laser energy depleted in the anterior segment and on the energy of the individual laser shot.

Laser cataract surgery aims at reducing such damage by replacing US energy consumption for nuclear workup by FSL energy. However, FSL energy as such may also potentially cause collateral damage to intraocular tissues by provoking release of prostaglandins (Schultz et al. 2013) and other inflammatory cytokines (Wang et al. 2016), chemokines and growth factors (Chen et al. 2015) as well as acidic shift (Rossi et al. 2015) and temperature rise (Mencucci et al. 2015) in the aqueous.

Endothelial cell loss (ECL) has most often been used as a parameter to quantify potentially harmful effects on ocular tissues. A significant reduction in ECL has been reported for LCS compared with MCS (Abell et al. 2014). However, apart from radicals in the aqueous, ECL is largely dependent on the direct mechanical impact of nucleus pieces set free during nucleus workup and carried along with the fluid stream (Miyata et al. 2002) and is thus highly influenced by the surgical technique, fluidic settings and ophthalmic viscoelastic devices used by the individual surgeon. Postoperative flare has also been used for comparison of MCS and LCS (Abell et al. 2013a,b; Liu et al. 2019). Laser flare photometry (LFP) provides accurate and reproducible quantification of subclinical alterations in the blood–ocular barrier (Tugal-Tutkun & Herbort 2010). However, phacoemulsification releases fine nucleus material into the anterior chamber, which may mimic flare and circulating cells postoperatively. This may partly explain the inconsistency in the published results (Abell et al. 2013a,b; Liu et al. 2019).

In contrast to the aforementioned parameters, macular thickness and volume changes are not influenced by any direct mechanical impact of sequestered or emulsified nuclear material circulating in the aqueous. Optical coherence tomography (OCT) has evolved into a highly precise and reproducible technique to quantify macular thickness and volume changes.

Macular swelling is a remote effect of inflammatory mediator release in the anterior segment. Apart from the aforementioned radical formation during phacoemulsification, such release is also caused by mechanical injury of the anterior lens epithelium (Nishi et al. 1992) during laser capsulotomy. This has been shown to be the main inducer of the significant increase in prostaglandin and interleukin levels in the aqueous reported for high-energy pulse lasers (Schultz et al. 2013, 2015). For the particular low-energy laser used in the present study, however, we have demonstrated that no such increase in the inflammatory mediator level occurs after laser capsulotomy and nucleus sectioning (Schwarzenbacher et al. 2020). Thus, potential differences in cytokine release–related postoperative macular swelling in this study should solely mirror differences in tissue stress and trauma during nucleus workup with and without FSL pretreatment.

Differences in the surgical technique and nucleus hardness, anterior chamber depth and the multitude of other individual parameters add to the variability in the reported results. Due to the multifactorial dependencies, exceptionally large study populations would be necessary to make statistically significant differences meaningful (Chang 2017). The number of eye required can be largely reduced by comparing eyes intraindividually, matching for nuclear hardness and using a standardized surgical technique.

We investigated the impact of FSL-assisted cataract surgery on US consumption and on the macula. For optimal comparability, we performed the study with a best possible standardized approach regarding the surgical technique in an immediately sequential bilateral surgery setting. Effective phacoemulsification time (EPT) was used to quantify US energy consumption with the US power limited to 30%. Because of its sensitivity and reproducibility, we chose macular thickness and volume as measured by high-resolution OCT as parameters to assess intraocular tissue stress or trauma exerted by the cataract procedure. Optical coherence tomography (OCT) measurements were performed preoperatively and at 1, 3 and 6 weeks postoperatively according to the delay in the appearance of macular swelling and cystoid macular oedema after cataract surgery. In a previous study, we have already used this method to detect and assess potential harmful effects of additionally performing a primary posterior capsulorhexis for after-cataract prevention (Stifter et al. 2008).

Materials and Methods

One hundred and twenty eyes of 60 patients were included in this prospective, randomized clinical trial for intraindividual comparison. The study was performed at the Department of Ophthalmology at the Vienna General Hospital (Medical University of Vienna, Austria). The inclusion criteria were bilateral age-related cataract, age 40 and older, visual potential of 20/30 or better in both eyes and no medical conditions such as rheumatic diseases or previous artery or vein occlusion in medical history and physical examination. The exclusion criteria were a history of ocular disease, preceding ocular surgery or trauma, relevant other ophthalmic diseases (macular degeneration or oedema, pseudoexfoliation, etc.), diabetes and any intraoperative complication. The study was approved by the Local Ethics Committee of the Medical University of Vienna, Austria (EK 1053/2018). All the research and measurements followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all subjects in this study.

An experienced certified physician performed a preoperative grading according to the Lens Opacities Classification System III (LOCS III) (Chylack et al. 1993). Nuclear opalescence was estimated and compared between partner eyes using a Haag-Streit BQ 900 biomicroscope with the slit lamp set at maximum intensity and a fixed angle. Participating patients were randomized into two groups at the screening date to receive either MCS or LCS in a randomized order. Before the investigation started, a randomization list was generated with Datinf Randlist software A (version 2.0, Datinf GmbH, Tübingen, Germany). Patients and investigators were masked to the surgery. A sealed envelope containing the randomization of each patient was handed to the surgeon in the operating room on the day of surgery to undergo either MCS or LCS. The examiner was unaware which type of surgery was to be performed on a given eye. All patients were operated by the same experienced surgeon (R. M.) using the same standardized technique. The same fluidics and longitudinal mode phacoemulsification settings were used for both procedures. To compensate for the weakness of EPT as the mere product of time and US power independent for the latter, linear US power release was limited to a maximum of 30%. Manual cataract surgery (MCS and LCS techniques were identical with the only difference that with LCS limbal incisions, circular opening of the anterior capsule and nucleus sectioning were performed by the FSL, whereas with MCS, manual blade incisions, needle capsulorhexis and nucleus division were done.

With MCS, a temporal 2.2 mm posterior limbal incision was created with a bevel-up metal blade and the aqueous exchanged by hydroxymethylcellulose 2%. Two paracenteses were made supero- and inferotemporally, and a digital image-guided 5.0–5.5 mm capsulorhexis centred on the 1st Purkinje image was performed with a bent needle. Hydrodissection and rotation of the nucleus were followed by manual fragmentation into four sectors and sector aspiration.

For nucleus workup, a special phaco needle was used (easyTip®2.2, in combination with an OS4 phaco machine, Oertli, Switzerland), which was designed to minimize US energy consumption by fully exploiting the potential of maximum fluidics ('ultrasound-assisted forced fluidics phacoaspiration') (Menapace & Di Nardo 2010). The phaco needle features a swollen tip with a 45° bevel and a slim 0.75-mm shaft with a small 0.45-mm bore, both connected by a conical transition zone. The strong bevel of the tip increases the size of the orifice and thus the holdability. The stepped internal transition of the large tip orifice into the small shaft bore increases the frontal projection plane and thus the energy transfer to attached nuclear material. Due to the increased internal flow resistance, the small shaft bore acts as an inbuilt surge break, thus allowing for maximum vacuum settings. The slim shaft conversely augments the cross-section of the infusion mantle along the sleeve. The resulting decrease in infusion flow resistance allows for maximum flow rates and thus followability. The sleeve openings are positioned in the plane of the bevel. Fluid pathways and US energy emission are thus directed into the same plane.

The manual phacoemulsification technique used in the MCS cases is described in the following: In the eye, the tip bevel is oriented horizontally. First, the nucleus is impaled by guiding the tip directly down into its core. With the full vacuum reached, a special phaco spatula (Bausch+Lomb REF 55485 nucleus divider) is introduced alongside the phaco needle tip and the nucleus split into two halves by extending the distal crack proximally ("ab interno nucleus cracking", Menapace & Di Nardo 2010). The nucleus is then rotated by 90 and 270° and the halves impaled and split into quadrants. For optimal workup of the fully separated quadrants, the flow rate of the peristaltic pump is increased to 60ml/min for ready occlusion of the trumpet-shaped mouth of the tip and a fast vacuum rise and the vacuum limit 650 mmHg to maximize linear US power coupling and aspiration force. After refilling the anterior chamber and capsular bag with methylcellulose 2%, the phaco needle orifice is positioned at the tip or flank of the quadrants. Upon activation of the pump, the nucleus chunk is quickly attracted and readily occludes the needle orifice. With the high flow rate used, vacuum quickly rises to the maximum. Linear US power delivery is chosen. Maximum US power is locked at 30% of the power range provided by the machine and the US power actually recalled by the surgeon limited to the minimum required to establish full occlusion and then to keep nucleus aspiration running should the aspiration needle be clogged by nucleus material. With the nucleus workup completed, cortex remnants are aspirated and a foldable hydrophobic acrylic intraocular lens (IOL) is injected into the capsular bag filled with a hyaluronic acid 1%. The latter is aspirated and the surgery finalized by hydration of the incisions and injection of 0.1ml cefuroxime 1% for intraocular infection prophylaxis.

Laser cataract surgery (LCS) was performed with the Femto LDV Z8 platform (Ziemer Ophthalmic Systems AG, Switzerland) with the surgeon sitting at the side of the patient's head. After docking the handpiece with its integrated laser optics to the eye, a 5.2 mm pupil-centred capsulotomy was created at a resection height of 0.6 mm and 90% laser power. The nucleus was then cut into six sectors using a safety distance to the capsule of 0.5 mm posteriorly and 0.4 mm peripherally as well as anteriorly and a laser power of 130%. A 2.3 mm clear corneal temporal incision and two 0.7 mm paracenteses were finally created supero- and inferotemporally with the FSL. The laser handpiece was removed and the operating microscope swung into position. The incisions were opened with a blunt-tip spatula and the aqueous exchanged for hydroxymethylcellulose 2%. The excised anterior capsule disc was extracted with capsulorhexis forceps. With the bevel of the pahco tip again turned sideward, the nasal sector of the nucleus was impaled from the centre and the radial FSL precut fully extended down to the posterior capsule and towards the equator using the spatula specified before. The lens was consecutively rotated by 60°, and the manoeuvre repeated until all six sectors were completely freed from residual posterior adhesions. The sequestered nucleus sectors were engaged and aspirated using the same high fluidics with minimum linear phaco power as with MCS. Cortex remnants were aspirated and the same type of IOL implanted. Intracameral cefuroxime prophylaxis concluded the surgery.

As a postoperative regimen, a combination of dexamethasone and gentamicin sulphate drops (Dexagenta, Ursapharm, Germany) were prescribed three times daily for 1 week and ketorolac drops (Acular, Pharm-Allergan, Austria) three times daily for 3 weeks. The primary end-point of the study and basis for sample size calculation was the change of central macular thickness (CMT) at 1 week, 3 weeks and 6 weeks postoperatively. Secondary outcomes were EPT, and central macular volume (CMV) and total macular volume (TMV) changes at 1 week, 3 weeks and 6 weeks postoperatively. The time frame of 6 weeks was chosen to match the 4–10 week delay in the development of macular swelling and appearance of cystoid macular oedema (Flach 1998; Bertelmann et al. 2012). A 512 × 128 macular cube scan was measured by a CIRRUS HD-OCT (ZEISS, Jena, Germany) and OCT images screened for changes in macular morphology and cystoid edema formation. Once evaluated as healthy, Spectral Domain OCT images were obtained through dilated pupils with Spectralis OCT (Spectralis Family Acquisition Module, V 6.16.6.0; Heidelberg Engineering, Heidelberg, Germany) with Heidelberg Eye Explorer (V 1.10.4.0; Heidelberg). A raster horizontal 20° × 20°, 49 B scans, with a reciprocal distance of 118 μm, and 15 frames averaged per B scan, adjusted on the fovea was obtained for both eyes of each patient to obtain CMT, CMV and TMV. The follow-up function of Heidelberg Eye Explorer software was used to measure the same area of interest in each follow-up visit.

Statistical evaluation

Statistical analysis was performed using SPSS V.23.0.0.3. Sample size calculation including dropouts suggested 120 eyes or 60 patients considering differences in macular thickness after MCS, as reported by Gharbiya et al. (2013), after 1 day and 1, 2, 4, 8, 12 and 24 weeks after MCS. According to these authors, the standard deviation of CMT is around 5.2 μm. A change in the mean of 2 μm (0.4 SD) is the minimal relevant difference we would be able to detect. With 80% power, a difference of 0.4 SD can be found with a paired t-test at two-sided significance level alpha=0.05 if the group size is at least 45 eyes per group. A surplus of 15 eyes was added to compensate for possible dropouts.

We defined three outcome parameters: CMT, CMV and TMV. We assessed normal distribution by histograms. If normally distributed, we investigated correlations between those parameters using Pearson's correlation, otherwise by Spearman correlation.

We then calculated individual linear mixed models with CMT, CMV or TMV as the dependent variable. For each of these models, we specified two random factors (RFs) to account for intrapatient correlation (=2 eyes from the same patient) and intraeye correlations (=multiple visits from the same eye). The RF for the eye was thus nested in the RF of the patient. Method, time point, axial length, LOCS grading (nuclear opalescence), EPT, age and the baseline value either of CMT, CMV or TMV, were defined as fixed factors. The interactions LOCS*EPT, age*LOCS, axial length*CMT/CMV/TMV at baseline and method*EPT were primarily included in the models. Residuals of the models were assessed for normal distribution by histograms.

To eliminate the expected strong association of the dependent parameters with their respective baseline value, we investigated CMT, CMV and TMV as change of each visit to baseline as the dependent parameter (week 1 to baseline; week 3 to baseline; week 6 to baseline) and, if normally distributed, we investigated correlations between these parameters using Pearson's correlation. For each of these parameters we calculated a linear mixed model with the same RF as described in the previous models (RF for eye nested in RF for the patient). Method, time point, axial length, LOCS grading, EPT and age were defined as fixed factors. The interactions LOCS*EPT, age*LOCS, axial length*CMT/CMV/TMV and method*EPT were primarily included in the models. Residuals of the models were assessed for normal distribution by histograms.

Results

No surgical complications occurred. Of the 60 randomized participants, 52 patients (36 female and 24 male patients) aged 71.0 ± 7.0 years completed the full follow-up, whereas 55 patients had at least one follow-up visit after the baseline assessment and surgery. Thus, these 55 patients were included in the statistical model which accounts for missing values. Results are presented as means±sd or medians [min; max]. According to the distribution of measured values, LOCSIII grading values were preferentially expressed as means, and EPT and CMT data as medians. Nuclear hardness according to the LOCS III classification was comparable in both groups (MCS: mean 2.44 ± 1.08, LCS: mean 2.50 ± 1.10, $p = 0.371$, Fig. 1).

Figure 2 shows US energy consumption as EPT values for the MCS and LCS groups. Median EPT was 1.40 seconds, range 0.2 to 8.3 in the MCS and 1.25 seconds, range 0.2 to 9.4 in the LCS group. The difference was not statistically significant ($p = 0.847$). The US power applied never exceeded 30 percent of the machine's possible maximum.

Median preoperative CMT was 276.50 [263.25; 289.75] μm in the MCS and 276.00 [262.00; 290.00] μm in the LCS group. Median preoperative TMV was 8.37 [8.23; 8.51] mm^3 in the MCS group and 8.37 [8.23; 8.51] mm^3 in the LCS group and thus identical.

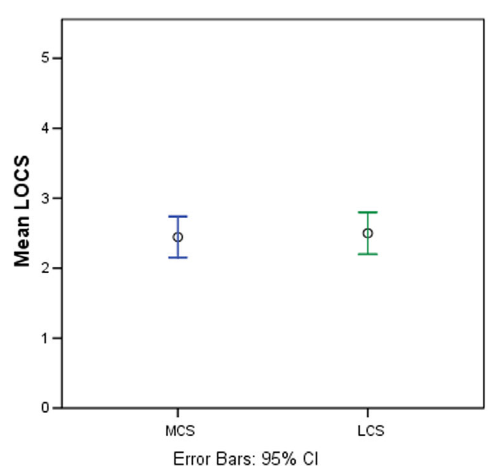

Fig. 1. Nuclear hardness according to LOCS III classification.

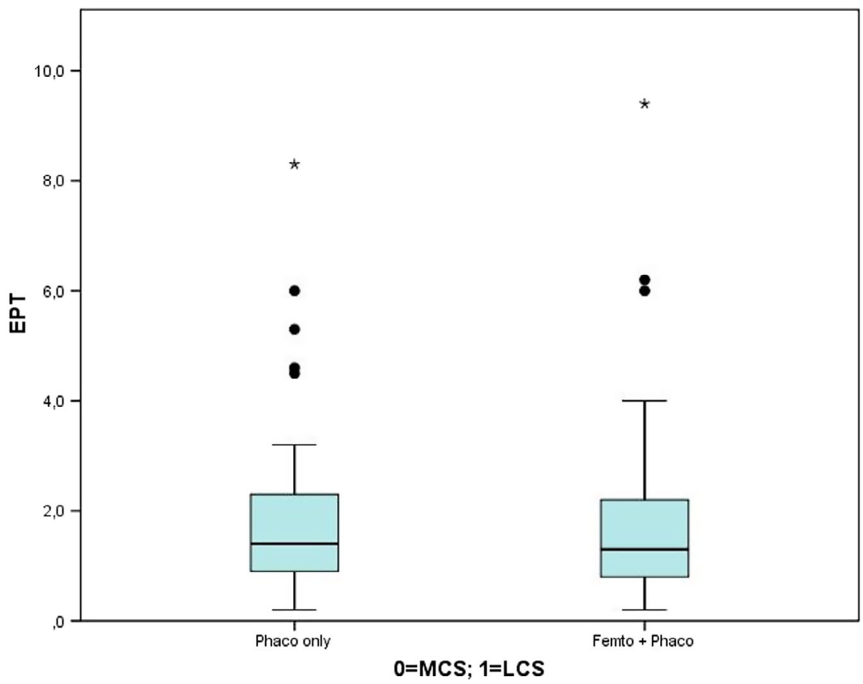

Fig. 2. Ultrasound energy consumption displayed as EPT.

Respective median postoperative CMTs were 278.00 [260.50; 288.00] versus 275.50 [264.00; 290.50] µm after 1 week, 279.50 [266.75; 292.25] versus 280.00 [266.50; 294.50] µm after 3 weeks and 280.50 [268.00, 293.75] versus 279.50 [264.75; 295.25] µm after 6 weeks. Respective median postoperative TMVs were 8.46 [8.34; 8.62] versus 8.49 [8.35; 8.63] mm^3 after 1 week, 8.58 [8.44; 8.72] versus 8.57 [8.43; 8.71] mm^3 after 3 weeks and 8.60 [8.46; 8.74] versus 8.61 [8.47; 8.75] mm^3 after 6 weeks. Figures 3 and 4 depict the course CMT and TMV over the full follow-up period. Mean preoperative CMT was 276.1 ± 21.1 µm in the MCS and 275.7 ± 22.4 µm in the LCS group. Respective mean postoperative CMTs were 275.9 ± 22.0 µm versus 275.7 ± 22.6 after 1 week, 280.0 ± 22.7 versus 279.8 ± 23.1 µm at 3 weeks, and 282.2 ± 23.5 versus 281.5 ± 24.2 µm at 6 weeks. There was no statistically significant difference found between LCS and MCS in CMT or TMS in any time point (p = 0.31 and p = 0.69). Central macular thickness (CMT) and CMV were highly correlated (R = 0.99, p < 0.001); however, CMT and TMV showed only a moderate correlation (R = 0.4, p < 0.001). We therefore omitted CMV as it was too similar to CMT. With change to baseline calculations, parameters were normally distributed, and the correlation between change of CMT and change of TMV improved (R = 0.74; p < 0.001). We then calculated four models: (1) CMT, (2) change of CMT, (3) TMV and (4) change of TMV, omitting CMV due to the high correlation with CMT. The interactions LOCS*EPT, age*-LOCS and axial length*CMT/TMV were not significant in any model and did not improve the model performances based on the corrected Akaike information criterion (cAIC). Thus, these interactions were omitted for the final models. The interaction method*EPT was not significant in any model but increased model performance and therefore remained within the final models. Results of each model are shown in Tables 1-4. Residuals were normally distributed for each individual model. Interestingly, CMT remained stable without significant change from baseline to week 1 (p = 0.63) (Table 1), whereas TMV increased already between baseline and week 1 (p < 0.001) (Table 2). Further continuous increase in both CMT and TMV was found after week 1 (all p < 0.001).

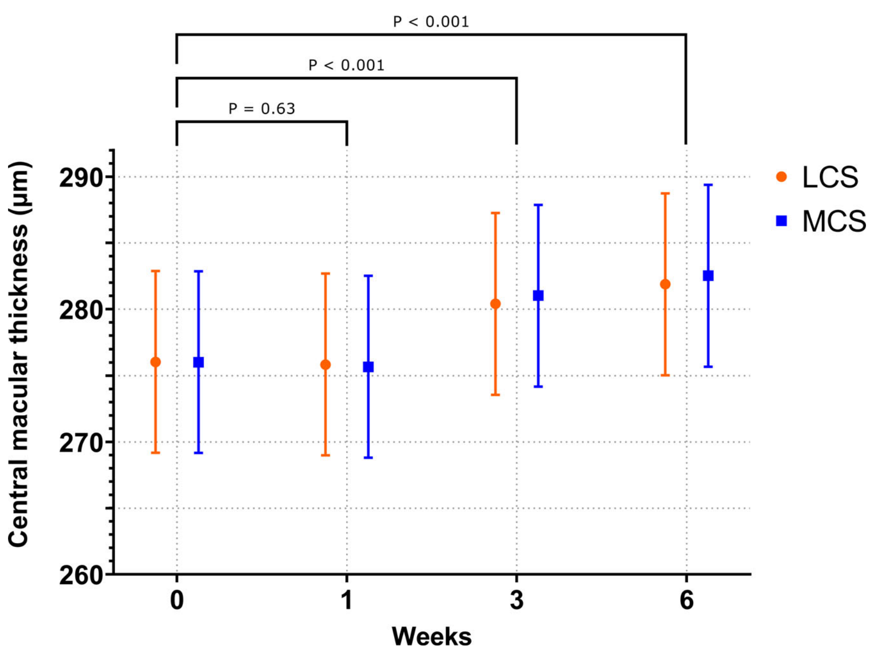

Fig. 3. Central macular thickness (CMT) development depicted as box plots. CMT in µm from preoperative (0), 1 week, 3 weeks and 6 weeks in the LCS and MCS group. p-Values pooled for the total cohort are shown from preoperative to 1 week, 3 weeks and 6 weeks, respectively. LCS = Laser cataract surgery; MCS = Manual cataract surgery.

Each individual OCT was also screened for morphological changes. No case of structural irregularities or signs of CME formation was observed.

Discussion

The US energy required for nucleus workup during cataract surgery largely depends on the hardness of the nucleus and the surgical approach. To assess the true benefit of FSL-assisted compared with conventional manual

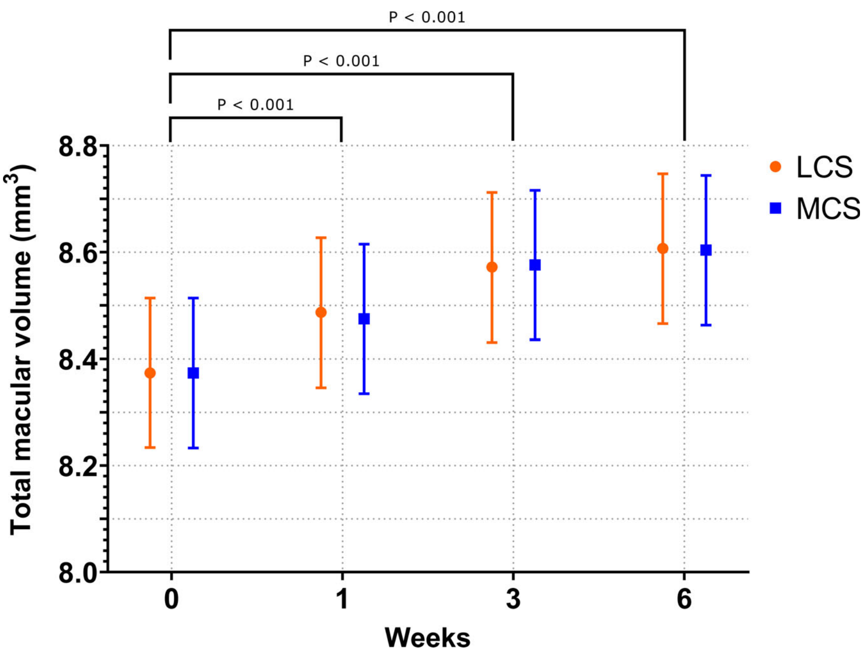

Fig. 4. Total macular volume (TMV) development depicted as box plots. TMV in mm^3 from preoperative (0), 1 week, 3 weeks and 6 weeks in the LCS and MCS group. p-Values pooled for the total cohort are shown from preoperative to 1 week, 3 weeks and 6 weeks, respectively. LCS = Laser cataract surgery; MCS = manual cataract surgery.

Table 1. Results for the linear mixed model with CMT as the dependent variable.

Parameter	Estimate	p-value	Lower 95% CI	Upper 95% CI
Method (LCS)	1.02	0.31	−0.98	3.03
Axial length	0.17	0.56	−0.41	0.76
LOCS	−0.22	0.48	−0.84	0.4
EPT	0.35	0.28	−0.28	0.99
Age	−0.01	0.9	−0.1	0.09
CMT baseline	1.02	<0.001	0.99	1.05
Week 1*	−0.27	0.63	−1.37	0.83
Week 3*	4.71	<0.001	3.61	5.82
Week 6*	6.19	<0.001	5.07	7.3

Interaction method*EPT p = 0.73.
CMT = central macular thickness; EPT = effective phacoemulsification time; LCS = laser cataract surgery; LOCS = lens opacities classification system.
* Compared with CMT baseline.

phacoemulsification, differences in nuclear hardness and variations in the surgical approach must be minimized. In this study, one surgeon performed all surgeries using a standardized surgical technique with fixed fluidic settings and identical nucleus sectioning techniques within bothe the MCS and LCS groups to workup medium hard nuclei as judged by an experienced examiner based on the LOCS III classification system. LCS and MCS were performed bilaterally in one session, and the type of surgery on the first eye was randomized.

The potential impact of an FSL to save US time and its possible side-effects depend on the laser technology. With the Ziemer Z8 LVD platform used for this study, the laser optics are integrated in the application handpiece. Compared with other machines with the laser optics separated from the suction device, this technology inherently reduces the focus length of the laser optics by a factor of 10 to 1cm while correspondingly augmenting the angle of aperture. As a result, the laser spot size is reduced to less than 2μm (Pajic et al. 2017) compared with 10 μm (Friedman et al. 2011) and the pulse energy to nanojoules compared with microjoules with conventional FSL platforms. Accordingly, the cavitation bubble size decreases (Ripken 2007). To still allow time-efficient tissue cutting, the laser spots are delivered at a frequency of megahertz, instead of kilohertz, which compensates for the reduced spot separation. Smaller size and overlapping localization of these low-energy spots result in much smoother edges of the tissue cuts (Williams et al. 2016) while producing less gas and reducing other side effects. These advantages of Z8 LDV low-energy high-frequency pulse laser technology have been substantiated in laboratory, animal and clinical studies. Low-energy pulses resulted in less lens epithelial cell death along capsulotomies (Mayer et al. 2014) and less collagen fibre damage (Riau et al. 2014) as well as reduced stromal cell death and inflammatory cell infiltration along corneal tissue cuts (de Medeiros et al. 2009).

With the low-energy laser platform used in our study, prostaglandin and other inflammatory aqueous cytokine levels remain low (Liu et al. 2019; Schwarzenbacher et al. 2020), whereas with conventional lasers working with comparably high-energy pulses at a low frequency, cytokine levels have been shown to increase by a multiple (Schultz et al. 2013).

Macular thickness is a well-defined parameter and a highly sensitive sensor for assessing tissue trauma by intraocular surgical procedures. Macular swelling develops in response to free radical formation which causes release of inflammatory cytokines and breakdown of the BAB. Significant anterior segment trauma may result in structural changes and oedema of the macula. Published findings on the impact of LCS and MCS on macular thickness and morphology vary. In a large prospective cohort case series comparison comprising 833 LCS and 458 MSC eyes, Ewe et al. (2015) using the Cirrus SD-OCT (Zeiss, Jena, Germany) found a fourfold higher CME rate of 0.8% in the laser group compared to 0.2% in the conventional group, and others reported similar CME rates (Conrad-Hengerer et al. 2014) using the Topcon 3D OCT-2000 (Topcon Corporation, Tokyo, Japan). Different acquisition protocols in the studies mentioned before may explain the varying results. However, we do believe that the study results are comparable even though different devices were used. Anterior chamber flare, a clinical consequence of BAB breakdown, was higher in the MCS group in a study by Abell et al.

Table 2. Results for the linear mixed model with TMV as the dependent variable.

Parameter	Estimate	p-value	Lower 95% CI	Upper 95% CI
Method (LCS)	0.01	0.69	−0.03	0.05
Axial length	−0.001	0.87	−0.01	0.01
LOCS	−0.003	0.67	−0.02	0.01
EPT	0.002	0.7	−0.01	0.02
Age	−0.002	0.14	−0.003	0.0005
TMV baseline	1.00	<0.001	0.96	1.04
Week 1*	0.17	<0.001	0.08	0.13
Week 3*	0.20	<0.001	0.18	0.22
Week 6*	0.23	<0.001	0.21	0.25

Interaction method*EPT p = 0.71.
EPT = effective phacoemulsification time; LCS = laser cataract surgery; LOCS = lens opacities classification system; TMV = total macular volume.
* Compared with TMV baseline.

Table 3. Results for the linear mixed model with CMT change to baseline as the dependent variable.

Parameter	Estimate	p-value	Lower 95% CI	Upper 95% CI
Method (LCS)	1.45	0.29	-1.23	4.13
Axial length	0.36	0.35	-0.40	1.12
LOCS	-0.24	0.57	-1.06	0.59
EPT	0.53	0.22	-0.32	1.37
Age	-0.02	0.77	-0.15	0.11
Change to week 3*	4.98	<0.001	3.84	6.12
Change to week 6*	6.49	<0.001	5.33	7.64

Interaction method*EPT p = 0.073.
CMT = central macular thickness; EPT = effective phacoemulsification time; LCS = laser cataract surgery; LOCS = lens opacities classification system.
* Compared with CMT change between baseline and week 1.

Table 4. Results for the linear mixed model with TMV change to baseline as the dependent variable.

Parameter	Estimate	p-value	Lower 95% CI	Upper 95% CI
Method (LCS)	0.01	0.70	−0.05	0.07
Axial length	−0.001	0.88	−0.02	0.02
LOCS	−0.004	0.67	−0.02	0.01
EPT	0.003	0.73	−0.01	0.02
Age	−0.002	0.14	−0.005	0.0007
Change to week 3*	0.09	<0.001	0.07	0.12
Change to week 6*	0.13	<0.001	0.10	0.15

Interaction method*EPT p = 0.75.
EPT = effective phacoemulsification time; LCS = laser cataract surgery; LOCS = lens opacities classification system; TMV = total macular volume.
* Compared with TMV change between baseline and week 1.

(2013a,b) but higher in the LCS group in the study by Liu et al. (2019). The latter reported that the LCS eyes, despite using a low-energy pulse laser, also exhibited higher levels of free radicals than the MCS group when not inhibited by preoperative NSAID medication.

Regarding the impact of LCS on CMT, published results also vary. Nagy et al. (2012) reported a significantly lower macular thickness in the inner retinal ring after one week for the laser group. This study, however, was small with only 13 MCS and 12 LCS eyes of different patients included. In a much larger study comparing 100 LCS and 76 MCS eyes, Abell et al. (2013a,b) observed an increase in outer zone macular thickness in both groups with a smaller increase in the laser group. In an intra-individual comparison of 101 patients, Conrad-Hengerer et al. (2014) found no change or difference in CMT up to 6 months postoperatively. In all three studies, a high-energy pulse laser was used, and nucleus hardness or nucleus workup technique and phaco machine specifications were not detailed, which limits the conclusiveness of the results.

We used a maximally standardized approach aiming at minimizing the energy input during laser pre-fragmentation and phacoemulsification by using a low-energy pulse FSL and a surgical technique combining an efficient nucleus sectioning with an US-saving high fluidics phacoaspiration technique. Effective phacoemulsification time (EPT), CMT and TMV were chosen as outcome measures.

Regarding EPT, studies have reported a significant reduction following FSL pre-fragmentation with the amount depending on the fragmentation pattern used (Conrad-Hengerer 2012; Uy et al. 2019). Interestingly, additional FSL pretreatment was not effective in reducing EPT in our study. Median EPTs were as low as 1.40 and 1.25 seconds in the manual and laser-assisted groups even though not using phaco-chop and torsional phaco known to reduce US time and energy compared with nucleus cracking or longitudinal phaco (Storr-Paulsen et al. 2008; Vasavada et al. 2010). Effective phacoemulsification times (EPTs) also favourably compare with the reported respective EPT of 4.9 ± 2.3 and 3.3 ± 1.4 seconds for MCS and LCS when using torsional phaco through a 2.7-mm incision for softer 1.9 ± 1.0 and 1.6 ± 0.6 mean-grade nuclei as reported by Liu et al. (2019). As in the latter study, the increase in the free radical level during phacoemulsification was shown to be significantly correlated with EPT, its reduction to minimum levels should help avoid macular swelling and CME formation.

This demonstrates the efficiency of ab interno cracking with an adapted spatula and forced fluidics sector aspiration (Menapace & Di Nardo 2010) for nucleus workup. While manual cracking fully separates the nucleus into sectors in one step, FSL prefragmentation has to leave a contiguous posterior lens plate untouched to avoid cutting into the posterior capsule. Also, the lens periphery outside the pupil margin cannot be presectioned. Thus, FSL prefragmentation still requires a second manual step to extend the cut to the posterior and equatorial capsule.

The small amount of additional US energy consumed during manual nuclear cracking is obviously outbalanced by this additional manoeuvre required to break up these residual adherences between the sectors created by the FSL prefragmentation. However, the profit of the additional use of a FSL may be much greater when combined with less efficient manual nucleus workup techniques, particularly when using low-flow and low-vacuum settings and classical divide-and-conquer techniques where two transversal grooves are sculpted in a shaving manner with the tip bevel unoccluded and oriented anteriorly.

Regarding macular changes in OCT, no statistically significant difference was found in CMT and CMV at any point in time and no statistically significant change during the follow-up. Total macular volume (TMV) statistically increased from week 1 to week 6 and CMT from week 3 to week 6. Chu et al. (2013) reported an increase in macular thickness of more than 30% in 8% of eyes 4 weeks after phaco surgery with significantly higher interleukin 1ß and other inflammatory cytokine levels. Liu et al. (2019) found that even with a low-energy platform, FSL laser-assisted cataract surgery was accompanied by significantly higher aqueous PGE2 levels and—though not statistically significantly—higher free radical activity compared to manual cataract surgery. Free radical formation was significantly associated with EPT (Liu et al. 2019). By reducing EPT to less than one half with even harder nuclei compared with the aforementioned study, the surgical setting of our study may per se reduce free radical formation and explain the significantly reduced cytokine release.

The two major findings and their clinical impact of this study may be summarized as follows:

1. The finding that EPT was low and not statistically different in both groups suggests

1a. The respective median EPT of 1.40 and 1.25 seconds in both groups for nuclei hardness with a mean hardness grade of around 2.50 reflects the high efficiency of the 2.2 mm high-fluidics longitudinal phaco technology in combination with the surgical technique for both manual and FSL-assisted nucleus workup. The generally low EPT and the lacking statistical difference in EPT between 6-sector FSL-precuts and manual 4-sector division used for nuclei with a mean nucleus hardness of 2.50 are proof of the surgical efficiency of high fluidic settings, which optimize followability, occlusion, vacuum rise time and US energy transfer under full vacuum.

1b. Manual cracking can be almost as efficient as FSL presectioning with its inherent need for completing sector separation in a second step of additional manual separation before aspiration. However, FSL prechopping may still help save US energy consumption with less efficient surgical settings. Presectioning the nucleus with an FSL inherently helps standardize nucleus workup. In addition to presectioning the nucleus into sectors, FSLs may execute almost any fragmentation pattern including small cubes, which largely reduces or even obviates the effort for manual division particularly in very hard nuclei. This, however, will inevitably translate into a significantly higher laser energy input accompanied by an increased depletion of inflammatory mediators, which may not be fully neutralized by NSAID medication (Liu et al. 2019) and the consequences of which on macula thickness need to be investigated in a separate study.

2. The finding that with similar EPTs in both groups, *no differences were found in central macular thickness and total macular volume between the LCS group and the MCT group* demonstrates that the additional pretreatment with a low-energy pulse laser including the capsulotomy has no negative impact on this sensitive intraocular structure. To compensate for the inherent shortcoming and bias of EPT by disregarding the actual power of the US released into the anterior chamber, US power was limited to a maximum of 30%.

A potential weakness of the study is that lens density was subjectively graded according to LOCS III and not objectively using Scheimpflug system–based software (e.g., Pentacam Nucleus Staging software, Oculus Optikgeräte GmbH, Germany). However, because all study patients were scheduled for bilateral surgery with one eye receiving MCS and the other LCS, the experienced examiner could intraindividually compare the optical nuclear opalescence and colour of the partner eyes. Furthermore, particularly with different patients, the actual hardness of the nucleus experienced during phacoemulsification may still vary, despite the same grading by automated Scheimpflug image analysis. Another minor weakness might be found in the fact that eight patients got lost to follow-up, resulting in 52 complete follow-up visits. This is compensated by a rather tolerant projected dropout rate in the study protocol and does ultimately not affect our statistical power.

Effective phacoemulsification time (EPT) is calculated as the mere product of US time and US power independent of the US power applied. This weakness was counterbalanced by limiting the retrievable US power to a maximum of 30% of the full US power range of the machine, which significantly contributed to the comparability of the EPT values obtained within the two groups. Another weakness is that the study reflects the results of one specific nucleus workup technique performed with a specific phaco tip and high fluidics. Although FSL prefragmentation did not significantly reduce effective phacoemulsification time in this study, this may still be true for harder nuclei or for less efficient manual nucleus workup techniques and phacoemulsification technologies, or other FSL technologies and fragmentation patterns.

In conclusion: With medium hard nuclei, manual 4-quadrant sectioning using the particular nucleus cracking and longitudinal high-fluidics phacoemulsification technique was similarly effective in terms of US energy consumption and equally safe in terms of CMT and volume changes compared with the additional use of a low-energy pulse FSL for 6-sector pre-prefragmentation.

Acknowledgments

L. Schwarzenbacher is a recipient of a doc fellowship of the austrian academy of sciences (award number 25082).

References

Abell RG, Allen PL & Vote BJ (2013a): Anterior chamber flare after femtosecond laser-assisted cataract surgery. J Cataract Refract Surg **39**: 1321–1326.

Abell RG, Kerr NM, Howie AR, Mustaffa Kamal MA, Allen PL & Vote BJ. (2014): Effect of femtosecond laser-assisted cataract surgery on the corneal endothelium J Cataract Refract Surg **40**: 1777–1783. Erratum in: J Cataract Refract Surg 2015; **41**:1128.

Abell RG, Kerr NM & Vote BJ (2013b): Toward zero effective phacoemulsification time using femtosecond laser pretreatment. Ophthalmology **120**: 942–948.

Bertelmann T, Witteborn M & Mennel S (2012): Pseudophakic cystoid macular oedema. Klin Monbl Augenheilkd **229**: 798–811.

Cameron MD, Poyer JF & Aust SD (2001): Identification of free radicals produced during phacoemulsification. J Cataract Refract Surg **27**: 463–470.

Chang DF (2017): Does femtosecond laser-assisted cataract surgery improve corneal endothelial safety? The debate and conundrum. J Cataract Refract Surg **43**: 440–442.

Chen H, Lin H, Zheng D, Liu Y, Chen W & Liu Y (2015): Expression of cytokines, chemokines and growth factors in patients undergoing cataract surgery with femtosecond laser pretreatment. PLoS One **10**: e0137227.

Chu L, Wang B, Xu B & Dong N (2013): Aqueous cytokines as predictors of macular edema in non-diabetic patients following uncomplicated phacoemulsification cataract surgery. Mol Vis **19**: 2418–2425.

Chylack LT Jr, Wolfe JK, Singer DM et al. (1993): The lens opacities classification system III. The longitudinal study of cataract study group. Arch Ophthalmol **111**: 831.

Conrad-Hengerer I, Hengerer FH, Al Juburi M, Schultz T & Dick HB (2014): Femtosecond laser-induced macular changes and anterior segment inflammation in cataract surgery. J Refract Surg **30**: 222–226.

Conrad-Hengerer I, Hengerer FH, Schultz T & Dick HB (2012): Effect of femtosecond laser fragmentation of the nucleus with different softening grid sizes on effective phaco time in cataract surgery. J Cataract Refract Surg **38**: 1888–1894.

de Medeiros FW, Kaur H, Agrawal V, Chaurasia SS, Hammel J, Dupps WJ Jr & Wilson SE (2009): Effect of femtosecond laser energy level on corneal stromal cell death and inflammation. J Refract Surg **25**: 869–874.

Dick HB & Schultz T (2017): A review of laser-assisted versus traditional phacoemulsification cataract surgery. Ophthalmol Ther **6**: 7–18.

Ewe SY, Oakley CL, Abell RG, Allen PL & Vote BJ (2015): Cystoid macular edema after femtosecond laser-assisted versus phacoemulsification cataract surgery. J Cataract Refract Surg **41**: 2373–2378.

Flach AJ (1998): The incidence, pathogenesis and treatment of cystoid macular edema following cataract surgery. Trans Am Ophthalmol Soc **96**: 557–634.

Friedman NJ, Palanker DV, Schuele G et al. (2011): Femtosecond laser capsulotomy. J Cataract Refract Surg **37**: 1189–1198. Erratum in: J Cataract Refract Surg **37**: 1742.

Gardner JM & Aust SD (2009): Quantification of hydroxyl radical produced during phacoemulsification. J Cataract Refract Surg **35**: 2149–2153.

Gharbiya M, Cruciani F, Cuozzo G, Parisi F, Russo P & Abdolrahimzadeh S (2013): Macular thickness changes evaluated with spectral domain optical coherence tomography after uncomplicated phacoemulsification. Eye **27**: 605–611.

Liu YC, Setiawan M, Ang M, Yam GHF & Mehta JS (2019): Changes in aqueous oxidative stress, prostaglandins, and cytokines: Comparisons of low-energy femtosecond laser-assisted cataract surgery versus conventional phacoemulsification. J Cataract Refract Surg **45**: 196–203.

Mayer WJ, Klaproth OK, Ostovic M, Terfort A, Vavaleskou T, Hengerer FH & Kohnen T (2014): Cell death and ultrastructural morphology of femtosecond laser-assisted anterior capsulotomy. Invest Ophthalmol Vis Sci **10**: 893–898.

Menapace R & Di Nardo S (2010): How to better use fluidics in MICS. In: Alió J & Fine H (eds.). Minimizing incisions and maximizing outcomes in cataract surgery. Berlin, Heidelberg: Springer 57–68.

Mencucci R, Matteoli S, Corvi A, Terracciano L, Favuzza E, Gherardini S, Caruso F & Bellucci R (2015): Investigating the ocular temperature rise during femtolaser lens fragmentation: an in vitro study. Graefes Arch Clin Exp Ophthalmol **253**: 2203–2210.

Miyata K, Nagamoto T, Maruoka S, Tanabe T, Nakahara M & Amano S (2002): Efficacy and safety of the soft-shell technique in cases with a hard lens nucleus. J Cataract Refract Surg **28**: 1546–1550.

Nagy ZZ, Ecsedy M, Kovács I, Takács Á, Tátrai E, Somfai GM & Cabrera DeBuc D (2012): Macular morphology assessed by optical coherence tomography image segmentation after femtosecond laser-assisted and standard cataract surgery. J Cataract Refract Surg **38**: 941–946.

Nishi O, Nishi K & Imanishi M (1992): Synthesis of interleukin-1 and prostaglandin E2 by lens epithelial cells of human cataracts. Br J Ophthalmol **76**: 338–341.

Pajic B, Cvejic Z & Pajic-Eggspuehler B (2017): Cataract surgery performed by high frequency LDV Z8 femtosecond laser: safety, efficacy, and its physical properties. Sensors (Basel) **17**: 1429.

Riau AK, Poh R, Pickard DS, Park CHJ, Chaurasia SS & Mehta JS (2014): Nanoscale helium ion microscopic analysis of collagen fibrillar changes following femtosecond laser dissection of human cornea. J Biomed Nanotechnol **10**: 1552–1562.

Ripken T. (2007): [Application of MHt-fs-lasers in ophthalmology and development of a therapeutic concept for the laser-assisted treatment of presbyopia.] Doctoral Thesis, Hannover.

Rossi M, Di Censo F, Di Censo M & Oum MA (2015): Changes in aqueous humor ph after femtolaser-assisted cataract surgery. J Cataract Refract Surg **31**: 462–465.

Schultz T, Joachim SC, Kuehn M & Dick HB (2013): Changes in prostaglandin levels in patients undergoing femtosecond laser-assisted cataract surgery. J Refract Surg **29**: 742–747.

Schultz T, Joachim SC, Stellbogen M & Dick HB (2015): Prostaglandin release during femtosecond laser-assisted cataract surgery: main inducer. J Refract Surg **31**: 78–81.

Schwarzenbacher L, Schartmueller D, Leydolt C & Menapace R (2020): Intra-individual comparison of cytokine and prostaglandin levels with and without low-energy, high-frequency femtosecond laser cataract pretreatment following single-dose topical NSAID application. J Cataract Refract Surg **46**: 1086–1091.

Stifter E, Menapace R, Neumayer T & Luksch A (2008): Macular morphology after cataract surgery with primary posterior capsulorhexis and posterior optic buttonholing. Am J Ophthalmol **146**: 15–22.

Storr-Paulsen A, Norregaard JC, Ahmed S, Storr-Paulsen T & Pedersen TH (2008): Endothelial cell damage after cataract surgery: divide-and-conquer versus phaco-chop technique. J Cataract Refract Surg **34**: 996–1000.

Takahashi H (2005): Free radical development in phacoemulsification cataract surgery. J Nippon Med Sch **72**: 4–12.

Tugal-Tutkun I & Herbort CP (2010): Laser flare photometry: a noninvasive, objective, and quantitative method to measure intraocular inflammation. Int Ophthalmol **30**: 453–464.

Uy HS, Chan PS, Gil-Cazorla R & Shah S (2019): Comparison of surgical parameters using different lens fragmentation patterns in eyes undergoing laser-assisted cataract surgery. Int Ophthalmol **39**: 2459–2465.

Vasavada AR, Raj SM, Patel U, Vasavada V & Vasavada V (2010): Comparison of torsional and microburst longitudinal phacoemulsification: a prospective, randomized, masked clinical trial. Ophthalmic Surg Lasers Imaging **41**: 109–114.

Wang L, Zhang Z, Koch DD, Jia Y, Cao W & Zhang S (2016): Anterior chamber interleukin 1β, interleukin 6 and prostaglandin E_2 in patients undergoing femtosecond laser-assisted cataract surgery. Br J Ophthalmol **100**: 579–582.

Williams GP, George BL, Wong YR, Seah X-Y, Ang H-P, Loke MKA, Tay SC & Mehta JS (2016): The effects of a low-energy, high frequency liquid optic interface femtosecond laser system on lens capsulotomy. Sci Rep **6**.14742.

Received on December 13th, 2020.
Accepted on July 1st, 2021.

Correspondence:
Rupert Menapace, MD, FEBO, Prof.
Department of Ophthalmology
Medical University Vienna
Waehringer Guertel 18-20
A-1090 Vienna
Tel: +43 1 40400 7931
Fax: +43 1 40180 1440
Email: rupert.menapace@meduniwien.ac.at