A randomised AI-supported long-term evaluation of a layer-by-layer macular thickness profile after manual and femtosecond laser cataract surgery

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Abstract

Objectives: To evaluate retinal thickening 18-months after low-pulse energy femtosecond laser-assisted (LCS) and manual cataract surgery (MCS) using artificial intelligence (AI)-based automated retinal layer segmentation.

Methods:

Design: Prospective, randomised, intraindividual-controlled study

Setting: Department of Ophthalmology, Medical University of Vienna.

Patient Population: 120 eyes of sixty patients with age-related cataract

Intervention: Bilateral same-day LCS and MCS in a randomised sequence.

Main Outcome Measure: Retinal thickness preoperative, after 1 week, 3 weeks, 6 weeks and 18 months in the central 1mm, 3mm, 6mm. Inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), total retinal thickness (TRT) and photoreceptor (PR) thickness were segmented from Spectralis optical coherence tomography (OCT) using automated AI retinal layer segmentation.

Results: Fifty-six patients completed the follow-up. LCS compared to MCS did not impact any of the investigated retinal layers at any follow-up visit (p>0.05). For the central 1mm, a significant increase in TRT was seen after 1 week followed by an elevated plateau thereafter. For the 3mm and 6mm, TRT increased only after 3 weeks and 6 weeks and decreased again until 18-months. TRT remained significantly increased compared to preoperative thickness (p<0.001). INL and ONL were the main causative layers for the total TRT increase. PR declined 1 week after surgery but regained preoperative values 18 months after surgery.

Conclusions: Low-energy femtosecond laser pre-treatment did not influence thickness of the retinal layers in any topographic area compared to manual high fluidic phacoemulsification. TRT did not return to preoperative values 18 months after surgery.

Introduction

Pseudophakic cystoid macular edema (CME), also known as Irvine-Gass syndrome, is one of the most common retinal disorders following cataract surgery. Since the introduction of phacoemulsification (phaco) in 1968, the incidence of CME has decreased significantly. However, an increase in macular thickness can still be observed due to inflammatory-mediated reactions after phaco. ¹⁻⁴

Inflammatory mediators like prostaglandins, cytokines, interleukins, and growth factors are known to be released from the anterior lens epithelial cells (antLEC) and the anterior uveal tissue induced by surgical trauma of cataract surgery, stimulating the breakdown of the blood-retinal-barrier (BRB) and subsequent
leakage of fluids through the retinal vessel-wall to the perifoveal retinal tissues. This postoperative inflammation induces the development of CME, indicating a conversion of the retinal layer manifesting as cystic changes and deterioration of visual acuity. CME recurs in a predictable pattern, beginning with cystic changes in the inner nuclear layer (INL), progressing to combined INL and outer nuclear layer (ONL) morphology, and may continue to involve subretinal fluid.

Currently, phaco chop and longitudinal high fluidics or torsional phaco are considered state-of-the-art providing optimum safety and efficiency. However, the latest novelty in cataract surgery remains the introduction of Femtosecond lasers (FSLs) in 2009. Laser-assisted cataract surgery (LCS) provides a perfectly shaped and centred anterior capsular opening and additionally may additionally reduce the consumption of potentially hazardous ultrasound (US) energy. Since the establishment of LCS, various studies have been conducted to explore whether postoperative macular thickening is influenced by this new surgical method with potentially lower ultrasound energy consumption compared to conventional cataract surgery.

This study aims to examine the pattern of postoperative macular thickening analysing spectral-domain coherence tomography (SD-OCT) volumes with precise artificial intelligence (AI) based automated intraretinal layer segmentation. To the best of our knowledge, this is the first time macular thickening was evaluated prospectively after cataract surgery including LCS in an 18 months’ follow-up.

**Methods**

120 eyes of 60 patients were included in this prospective, randomised controlled trial. The study was performed at the Department of Ophthalmology at the Vienna General Hospital (Medical University of Vienna, Austria). Inclusion criteria were bilateral age-related cataract, age 40 and older, no pathologic medical conditions such as rheumatic diseases or previous artery or vein occlusion in medical history and physical examination. Exclusion criteria were a history of ocular disease, preceding ocular surgery or trauma, relevant other ophthalmic diseases (macular degeneration or edema, pseudoexfoliation, etc.), diabetes and any intraoperative complication or preoperative use of topical or systemic steroidal or nonsteroidal anti-inflammatory drugs (NSAIDs). The protocol was approved by the local ethics committee (EK 1053/2018) and registered at ClinicalTrials.gov (registration number: NCT03465124). All the research and measurements followed the tenets of the Declaration of Helsinki and written informed consent was obtained from all subjects in this study.

Participating patients were randomised into two groups at the screening date to receive either MCS or LCS in a randomised order. Before the investigation started, a randomisation list was generated with the Datinf Randlist software A (version 2.0, Datinf GmbH, Tübingen, Germany). Patients and investigators were masked to the surgery. A sealed envelope containing the randomisation 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 the 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 described in a previous
The same fluidics and longitudinal mode phacoemulsification settings were used for both procedures.

As a postoperative regimen, a combination of dexamethasone and gentamicin sulfate drops (Dexagenta, Ursapharm, Germany) were prescribed 3 times daily for 1 week and ketorolac drops (Acular, Pharm-Allergan, Austria) 3 times daily for 3 weeks.

Endpoint of the study was the change of central macular thickness (CMT) and four specific retinal layers at 1 week, 3 weeks, 6 weeks and 18 months postoperatively. The chosen layers were the inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL) and the photoreceptor layer (PR) as well as the total retinal thickness (TRT). Photoreceptor layer was defined between the inner border of the ellipsoid zone and the inner border of the retinal pigment epithelium and was segmented using an in-house developed and previously published AI-algorithm.\textsuperscript{13}

The macular layers were segmented from images obtained from 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° x 20°, 49 B scans, with a reciprocal distance of 118µm, and 15 frames averaged per B scan, adjusted on the fovea was obtained for both eyes of each patient. The automated algorithm was used to segment total retinal thickness (internal limiting membrane to Bruch's membrane), INL, OPL, ONL and PR on each OCT B-Scan. For the TRT, INL, OPL and ONL we used the IOWA reference algorithm. For the PR thickness, the in-house developed algorithm was used.\textsuperscript{13–15}

Sample size calculation including dropouts suggested 120 eyes considering differences in macular thickness after MCS. According to published literature, the standard deviation of CMT is around 5.2µm. Hence, a change in the mean of 2µm (0.4 SD) was defined as 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 were included into the study protocol to compensate for possible dropouts.

To investigate the differences in OCT measurements, linear mixed models (LMM) were calculated with each thickness measurement as the dependent variable. Five retinal OCT measurements were used in the LMM (TRT, INL, OPL, ONL, PR) and measurements were compared within three topographic areas (central 1mm, total 3mm and total 6mm). For each model, the thickness variable was specified as the outcome. Since two eyes and multiple visits were included from the same patient two random factors were defined. The random factor for the eye was then nested in the random factor for the patient ID. Age and each respective baseline value was included as continuous fixed factors. Method, sex, eye laterality and visit were specified as nominal fixed factors. An interaction term of Method*visit was specified to investigate differences between visits within each method group. Pairwise posthoc testing was performed applying Bonferroni correction for multiple testing. A p-value < 0.05 was considered statistically significant.
Results

In total, 120 eyes from 60 patients were included in the original study between March 2018 to January 2019. 112 eyes from 56 patients completed the 18 months follow-up visit and were included in the statistical evaluation for this study. Mean patient age at baseline was 71.2 ± 6.9 years. Out of the 56 patients 36 (64.3%) were female. The effective phacoemulsification time did not differ between LCS and MCS (p = 0.847).

The thicknesses of the total retinal at each time point are shown in Table 1. The tables for INL, OPL, ONL and PR thicknesses are presented in the supplemental files (Table S1-S4).

Table 1
Total Retinal Thickness (TRT) in the central 1mm, 3mm, 6mm.

<table>
<thead>
<tr>
<th>Macular area</th>
<th>1mm</th>
<th>3mm</th>
<th>6mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of surgery</td>
<td>MCS</td>
<td>LCS</td>
<td>MCS</td>
</tr>
<tr>
<td>Preoperative</td>
<td>284.64 (95% CI: 272.77, 296.51)</td>
<td>284.60 (95% CI: 272.73, 296.46)</td>
<td>323.43 (95% CI: 322.20, 324.66)</td>
</tr>
<tr>
<td>1 week</td>
<td>285,126 (95% CI: 273.12, 297.00)</td>
<td>284,986 (95% CI: 273.12, 296.85)</td>
<td>326.91 (95% CI: 325.68, 328.13)</td>
</tr>
<tr>
<td>3 weeks</td>
<td>290.29 (95% CI: 278.42, 302.16)</td>
<td>292.34 (95% CI: 280.48, 304.20)</td>
<td>331.33 (95% CI: 330.10, 332.56)</td>
</tr>
<tr>
<td>6 weeks</td>
<td>291.50 (95% CI: 279.62; 303.38)</td>
<td>291.49 (95% CI: 279.61; 303.37)</td>
<td>331.96 (95% CI: 330.70; 333.23)</td>
</tr>
<tr>
<td>18 months</td>
<td>288.85 (95% CI: 276.91; 300.79)</td>
<td>289.49 (95% CI: 277.56; 301.42)</td>
<td>328.68 (95% CI: 327.27; 330.08)</td>
</tr>
</tbody>
</table>

MCS = Manual Cataract Surgery; LCS = Laser Cataract Surgery

For TRT a significant impact of baseline value was found in each zone's mixed model (1mm, 3mm and 6mm, all < 0.001). The use of LCS compared to MCS did not differ in any of the investigated areas (all > 0.05). Sex only showed a significant impact in the 3mm area (p = 0.043) with an overall thicker TRT in men (329.19, 95%CI: 328.30, 330.09 vs. 328.03, 95% CI: 327.39, 328.68). The sex difference remained insignificant in the 1mm and 6mm area (both p > 0.05). Interestingly, a significant difference was found
for the visit number with an increase to week 3, followed by a plateau until week 6 with a slight decrease thereafter (Fig. 1). For 1mm, there was no difference between baseline and week 1 (p > 0.05) and between week 3, week 6 and month 18 (all p > 0.05). For 3mm, there was a significant difference already from baseline to week 1 (p < 0.001). However, the plateau between week 3 and 6 showed no difference (p > 0.05), whereas the subsequent decrease in TRT was again significant (p < 0.001), however compared to baseline TRT remained significantly increased 18 months after surgery in all areas (all p < 0.001). The same course of TRT was found in the 6mm area. TRT was

The INL thickness was highly significantly associated with the INL thickness at baseline (all zones p < 0.001). The surgery method did not impact INL thickness. The only significant parameter impacting INL thickness was visit number. For the 1mm area the increase showed significant differences to baseline at week 3 (p < 0.001) and reached again a plateau for week 6, which was significantly different to baseline (p = 0.014) but not to week 3 (p > 0.05). For the 18 months visit INL thickness in the central 1mm declined slightly, however the measurement was not significantly different to baseline any longer, but also not to the plateau values (all p > 0.05). A similar course is seen for the 3mm area, however the increase showed already significant values for the 1-week visit (p < 0.001) and still showed a difference at the month 18 visit (p < 0.001 compared to baseline, but p > 0.05 against all other visits). In the 6mm area the first significant increase is followed by a peak at week 3 and a significant decline thereafter. The 18 months visit showed significant differences to baseline (p < 0.001) and to week 3 (p = 0.005) and week 6 (p = 0.047).

The only factor associated with OPL thickness was ONL thickness at baseline (p > 0.001). Surgical method and visit number were not associated with OPL thickness in the central 1mm, 3mm or 6mm (all p > 0.05).

The thickness of the ONL was significantly associated with its baseline value in all zones (all p < 0.001). Surgical method did not impact ONL thickness and sex only had an impact in the central 1mm with men having a thicker ONL (107.82, 95%CI: 101.79, 113.90 vs. 105.35, 95% CI: 100.52, 110.18). In the central 1mm ONL thickness increased from week 1 to week 3 (p < 0.001) and remained on a plateau from thereon. The 18 months visit was insignificantly different to week 6 (p > 0.05), but significantly different to baseline and week 1 (p = 0.027 and p = 0.031, respectively). In the 3mm area the significant increase started already with week 1 (p = 0.015) and increased even further to the plateau at week 3 and 6. Thereafter, a significant decrease occurred (p = 0.029 and p < 0.001 compared to week 3 and 6, respectively), but month 18 remained significantly increased compared to baseline (p < 0.001). The same course was true for the 6mm area.

The baseline value for PR thickness was also associated with the PR thickness throughout the follow-up. The surgical method did not have an impact on PR thickness. Interestingly, a decrease in PR thickness is seen 1 week after surgery which is significant for each zone (all p < 0.001). Week 1 was significantly different to all other visits in the 3mm and 6mm areas (all p < 0.05 in comparison to visit 2 = week 1). In
the central 1mm there was no difference between week 1 and month 18 (p > 0.05), however, there was also no difference between baseline and month 18 (p > 0.05).

Discussion

It is known that modern cataract surgery affects the retinal layers after surgery, even when performed uneventful and atraumatically. In a previous study we could demonstrate clear evidence that there is no difference in central macular thickness between femtosecond laser-assisted cataract surgery (LCS) and conventional manual phacoemulsification (MCS) up to 6 weeks after surgery. In this study, we evaluated the thickness of the separate retinal layers as well as the total macular thickness up to 18 months after performing LCS and MCS simultaneously in both eyes in 56 patients. We could observe a statistically significant increase in the inner nuclear layer (INL), outer nuclear layer (ONL) and total retinal thickness (TRT) at the latest from three weeks onward after LCS and MCS but no increase in the outer plexiform layer (OPL). There was a modest decrease in thickening seen after six weeks and 18 months but all affected retinal layers did not reach preoperative thickness values. In fact, the macular thickening reached statistically significance and persisted in the entire follow-up period, especially in the perifoveal 1–3 mm zone. Interestingly, the photoreceptor layer (PR) declined significantly one week after surgery and reached preoperative values again after three weeks. There was no significant difference found at any time point between LCS and MCS. Ultrasound energy input as expressed by effective phacoemulsification time had been comparable in both groups.

Macular thickness is a highly sensitive parameter for assessing tissue trauma due to intraocular surgical procedures. The pathogenesis of postoperative macular thickening is yet to be fully explored and it is thought to be multifactorial. However, it is evident that the macular swelling occurs as a response to free radical formation associated with the release of inflammatory mediators, chemokines, and cytokines, inducing the breakdown of the blood-retinal-barrier (BAB) and an increased vascular permeability. Moreover, significant anterior segment trauma may cause structural changes and macular edema. Published findings regarding the impact of LCS and MCS on macular swelling and morphology vary. Menapace et al. using a low-energy pulse laser reported no case of CME when comparing LCS and MCS using Spectralis SD-OCT (Family Acquisition Module, V 6.16.6.0; Heidelberg Engineering, Heidelberg, Germany). In contrast, Ewe et al. using a high-energy pulse laser reported a fourfold higher CME rate of 0.8% in the femtosecond laser group compared to 0.2% in the conventional phaco group in a large prospective cohort case study comprising 833 LCS and 458 MCS eyes using Cirrus SD-OCT (Zeiss, Jena, Germany) even though ultrasound energy input was lower in the LCS eyes. Different acquisition protocols may explain the varying results in the studies mentioned before. In a study by Abell et al., anterior segment flare in consequence of BAB breakdown was higher in the MCS group differing from the results published by Liu et al. with higher chamber flare in the LCS group. Despite using a low-energy pulse laser, the latter reported that the LCS eyes also exhibited higher levels of free radicals and inflammatory mediators than the MCS group when no inhibition by preoperative NSAID medication was undertaken. Even though preoperative NSAIDs were also not used in our study, the resulting release of
free radicals and inflammatory mediators may explain an increase in macular thickness despite using a low-pulse energy femtosecond laser and postoperative topical NSAIDs.

Regarding the impact of LCS on CMT, studies have reported different patterns. Kurt et al. reported that macular thickening begins with cystic changes in the INL progressing to combined INL and OPL thickening, and may even continue to involve subretinal fluid. Postoperative CME occurs due to pro-inflammatory cytokines, prostaglandins and growth factors inducing retinal mid-capillary plexus hyperpermeability and affecting the INL due to the bordering branches of the mid-capillary plexus. Sigler et al. found that structural changes at this layer occur early in the course of the disease. The occurrence of isolated INL cystic change in normal fellow eyes supports the hypothesis that inflammatory mediators induced by mechanical trauma may either enter the bloodstream or affect the contralateral eye via the chiasmal pathway. As the latter study reported, bordering layers react structurally consistently due to extracellular fluid exiting the mid-capillary plexus of the INL. The following macular thickening and structural changes of the ONL, OPL, and PR may be induced by the connectivity of the superficial (SCP), middle (MCP), and deep retinal capillary plexus (DCP). While SCP was reported to supply the nerve fibre and ganglion cell layer, the location of MCP was defined at the boundary of INL and the inner plexiform layer (IPL). At the edge of the INL and OPL, the DCP represents the vascular supply. Exploring the release of inflammatory mediators in these three retinal vascular plexuses and the distribution of inflammatory mediators in the bloodstream, may help reduce the progression of postoperative macular disease.

Published results vary regarding macular thickening in different perifoveal areas (inner 1mm, 1-3mm circle, 3-6mm circle). Nagy et al. observed a significantly lesser thickness in the inner retinal zone after one week for the LCS group compared to MCS group but the study was conducted in a small sample size of only 12 and 13 eyes per group. In a larger study, Abell et al. included 100 LCS and 76 MCS eyes and observed an increase in thickness of the outer macular area with a smaller increase in the LCS group compared to MCS. Conrad-Hengerer et al. reported no difference or change in CMT up to 6 months postoperatively, observing 101 patients in an intra-individual study between LCS and MCS. All three mentioned studies comparing central macular thickness after LCS and MCS used a high-energy pulse femtosecond laser in contrast to the low-energy high-frequency pulse laser technology used in the present study.

In this study, an increase in the macular thickness of INL and ONL can be observed but these changes were only significant in the 1-3mm perifoveal area at the postoperative three-week follow-up. Moreover, macular thickening of the ONL, especially in the 1-3mm circle, was seen up to 6 weeks after LCS and MCS. PR thickness was declining up to the first follow-up visit, with a subsequent rebound up to 3 weeks postoperatively reaching preoperative thickness values and remaining on preoperatively values thereafter. This first-visit change of the outermost layers was also explored by Kurt et al. with a subsequent stable PR thickness after the first follow-up visit one week postoperatively. OPL was the only layer with a minor decrease of thickness after cataract surgery, especially in the 1-3mm perifoveal circle but no statistical significance was observed. However, Kurt et al. also reported, that the outermost layers like OPL and the
retinal pigment epithelium (RPE) remained most stable after cataract. Regarding the development of TRT, a statistically significant increase was found in CMT in all perifoveal areas, specifically in the 1-3mm perifoveal zone with maximum values at the 6-week postoperative follow-up visit, and a subsequent slight decrease without reaching preoperative thickness levels after 18 months. These findings may be useful for understanding the pathophysiological pathway of CME as well as the impact of inflammatory mediators on the development of structural changes of CMT due to phacoemulsification.\textsuperscript{1,2}

Regarding the follow-up period, results analysing the dynamics of macular thickness after cataract surgery also vary. Yilmaz et al. included 65 eyes with follow-up visits at 1 week postoperatively and 1, 3, 6 and 12 months after cataract surgery.\textsuperscript{22} During the one-year follow-up in this prospective study, the effect on macular thickening due to uncomplicated cataract surgery was reported to be transient with macular thickness increasing during the first three weeks and subsequently reaching preoperative thickness values up to six months postoperatively. Recent studies also evaluated an increase in CMT after the 3–6 months follow-up and subsequent regression without reaching preoperative levels.\textsuperscript{2,23} In our intra-individual study, we also reported similar results with a significant increase in TRT up to 6 weeks postoperatively and subsequently declining macular thickness without reaching baseline values.

A limitation of the study is the use of topical NSAIDs three times daily for the first three weeks after surgery. However, the topical postoperative regimen used in this study represents a real-world setting.

In conclusion, this study presents the macular thickness profile 18 months after LCS using a low-energy FSL and ultrasound-saving high fluidics MCS. The biggest increase in CMT was observed after three and six-weeks in both groups (LCS and MCS) without any difference between the groups. After the six-weeks visit, a slight decrease without reaching preoperative levels was seen in all layers except the OPL. The overall postoperative retinal thickness increase was more prominent in the 1-3mm perifoveal area than in the 1mm circle. The PR layer was temporarily thinned 1 week after surgery with an immediate subsequent recovery. The results suggest that long-term follow-up studies of more than 18 months are needed to evaluate whether partial and total retinal changes return to preoperative levels or remain permanently increased possibly due to a continued release of inflammatory mediators after state-of-the-art cataract surgery, independent if LCS or MCS is performed.

**Declarations**

The authors declare that they have no conflict of interest.

**FUNDING**

None of the authors has a financial interest in any material or method mentioned.

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Figures
Figure 1

Legend not included with this version.

Supplementary Files

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• SupplementTables.docx