Comparison of changes in corneal endothelial cell density and central corneal thickness between conventional and femtosecond laser-assisted cataract surgery: a randomised, controlled clinical trial

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ABSTRACT

Background/Aim To identify changes in endothelial cell density (ECD) and central corneal thickness (CCT) in eyes undergoing femtosecond laser-assisted cataract surgery (FLACS) compared with conventional phacoemulsification surgery (CPS).

Methods This is an intraindividual randomised, controlled clinical trial. One eye was randomised to receive FLACS, while the contralateral eye of the same patient received CPS. The femtosecond laser pretreatment included creating main and side-port corneal incisions, capsulotomy and lens fragmentation. Non-contact endothelial cell microscopy and pachymetry were performed preoperatively and at postoperative day 1, week 1, month 1 and month 3.

Results A total of 134 paired eyes from 67 patients were included in the analysis. ECD was not significantly different between the two groups at either postoperative month 1 (2370±580 cells/mm^2 and 2467±564 cells/mm^2 in FLACS and CPS groups, respectively; p=0.18) or at postoperative month 3 (2374±527 cells/mm^2 and 2433±526 cells/mm^2 in FLACS and CPS groups, respectively; p=0.19). No significant difference was observed in the mean CCT values between the two groups over the follow-up period (p>0.05).

Conclusion Postoperative corneal ECD and CCT were comparable between FLACS and CPS during the 3 months' follow-up period.

INTRODUCTION

Cataract remains the leading cause of reversible blindness worldwide. Since cataract is largely age related, the demand on cataract surgery will likely continue to grow with the globally observed increase in life expectancy and population ageing. Advancements in surgical equipment and techniques have made cataract surgery one of the safest in the clinical practice.[1] Currently, phacoemulsification is the standard surgical technique used in the developed world.[2] As the field continues to advance, newly developed technology should prove non-inferior, at minimum, to warrant adoption.

Although femtosecond laser (FL) has long been used in ophthalmic surgery, its use in cataract surgery is relatively recent. This technology uses ultrashort pulses of near-infrared light to disrupt tissues with micron precision, minimising collateral tissue damage.[3] Initial studies reported its intraoperative and postoperative advantages over conventional phacoemulsification surgery (CPS),[4–7] with several reports suggesting a reduction in effective phacoemulsification time (EPT) and cumulative dissipated energy (CDE).[8–12] Higher EPT and CDE values are known to be associated with an increased risk of corneal endothelial cell injury intraoperatively and corneal oedema postoperatively.[13–15] Thus, with the reduction of endothelial injury, it was postulated that the use of FL in cataract surgery may shorten the recovery period and improve visual outcomes.[1]

While theoretically conceivable, empirical evidence on the advantages of femtosecond laser-assisted cataract surgery (FLACS) over CPS has shown varying results. In a recent systematic review and meta-analysis, several postoperative outcomes were found to be comparable between FLACS and CPS.[16] In addition, another systematic review found published clinical trials to be at an unclear or high risk of bias.[17] With that in mind, we conducted this study to compare changes in postoperative endothelial cell density (ECD) and central corneal thickness (CCT) in paired eyes from the same subjects undergoing FLACS and CPS. The study also sought to explore correlations among preoperative and intraoperative parameters, such as EPT and CDE, in each of the treatment groups.

MATERIALS AND METHODS

This randomised, controlled clinical trial was conducted in accordance with Health Insurance Portability and Accountability Act regulations. The trial was registered at ClinicalTrials.gov (NCT02096627). Patients were enrolled from April 2015 to March 2018 and provided written informed consent to participate in the study. Patients were eligible for enrolment if they were ≥18 years old, had bilateral visually significant cataract and were able to attend follow-up for at least 3 months postoperatively. Patients with Fuchs' corneal endothelial dystrophy, other ocular pathology and/or previous/concurrent ocular surgery were excluded to prevent the inclusion of factors (eg, difficulty obtaining specular counts, endothelial decompensation propensity and longer postoperative oedema) that could confound the examined parameters

Table 1 Capsulotomy, lens-softening and corneal incision patterns for the femtosecond laser pretreatment procedure

Parameter	Value
Capsulotomy	
Diameter (mm)	5.5
Capsule delta up (µm)	300
Capsule delta down (µm)	325
Energy (µJ)	5.00
Tang spot separation (µm)	5
Layer separation (µm)	4
Lens fragmentation	
Diameter (mm)	
Chop	5.2
Cylinder	4.0
Lens anterior offset (µm)	500
Lens posterior offset (µm)	800
Energy (µJ)	7.00
Cuts, n	3
Spot separation (µm)	14
Layer separation (µm)	14
Primary and secondary incisions	
Energy (µJ)	4.00

and to minimise variability unrelated to the herein examined procedures.

For each patient, the worse seeing eye was randomised by the type of procedure into either FLACS or CPS using an online random number generator. Then, the contralateral, better seeing eye was automatically assigned to the alternate surgery type. On the day before the surgery, the surgeon was informed about the type of procedure to use in each eye. All surgeries were performed by the same surgeon (YJD) at an academic tertiary referral centre.

In the FLACS group, pretreatment was performed with the LenSx laser (Alcon Laboratories, Fort Worth, TX, USA). After successful docking of the laser-patient interface, spectral domain optical coherence tomography imaging of the anterior segment was performed. Images of the intraocular structures were automatically identified. The surgeon confirmed each step of the procedure in accordance with the necessary safety margins. After that, the laser treatment was initiated and included creating a 5.5 mm capsulotomy, lens fragmentation (LenSx pattern: concentric cylinders and segment cuts), two-plane 2.8 mm main corneal wound and one-plane 1.2 mm side-port incision (table 1). Once the FL pretreatment was completed, phacoemulsification was performed using the Infiniti Vision System (Alcon Laboratories). The laser-cut side-port and main incisions were opened with a Sinskey hook. After instillation of anaesthetic and mydriatic solutions, dispersive ophthalmic viscosurgical device (OVD) (Viscoat, Alcon Laboratories) was injected into the anterior chamber to protect the endothelium. The anterior capsule was removed with Utrata forceps (Katena Products, Denville, NJ) and was followed by hydrodissection. The surgery was then completed with standard phacoemulsification procedure with a pop-and-chop technique. The remaining cortex was removed with coaxial irrigation/aspiration. Cohesive OVD (Provisc, Alcon Laboratories) was injected to expand the anterior chamber and capsular bag, followed by intraocular lens (IOL) implantation. Stromal hydration was applied to close the corneal incisions at the end of the procedure. A combination steroid-antibiotic ointment was placed on the eye and, then, the eye was covered with a patch.

In the CPS group, a one-plane 1.2 mm paracentesis and a two-plane 2.75 mm main incision were made using disposable keratome knives. A cystotome was used to incise the anterior capsule, and a continuous curvilinear capsulorhexis was completed using Utrata forceps (Katena Products) through the main incision. The remaining steps were similar to those described in the FLACS group above.

Postoperatively, all patients received the same treatment regimen consisting of an antibiotic four times a day for 1 week. In addition, steroids and non-steroidal anti-inflammatory drops were administered four times a day during the first week, which were gradually tapered over the next 3 weeks.

A research assistant timed all intraoperative steps (operating room (OR) time). The starting point in the CPS group was the creation of the first corneal incision (paracentesis), whereas in the FLACS group, it was defined by the opening of the corneal incisions previously made by FL. Time measurement was stopped after hydration and closure of the incisions. Data on EPT, CDE and amount of balanced salt solution (BSS) use were obtained at the end of each case.

The primary outcomes of the study included changes in postoperative ECD and CCT. Secondary outcomes targeted intraoperative parameters and included EPT, CDE, amount of BSS use and OR time, as well as intraoperative complications. Postoperative outcomes were measured at 1 day (POD1), 1 week (POW1), 1 month (POM1) and 3 months (POM3) postoperatively. Nuclear sclerosis (NS) was graded during slit lamp examination in accordance with the Lens Opacities Classification System III (LOCS III).[18] Central corneal endothelial cell counts and CCT were assessed using a non-contact specular microscope (CellChek, Konan Medical, Irvine, CA). Central corneal endothelial cell counts were either made automatically or manually by an experienced technician (depending on image clarity and the ability of the machine to recognise endothelial cells). Endothelial cell loss (ECL) was expressed as the percentage of preoperative to postoperative change in ECD over the preoperative ECD. ECD and ECL data from a POD1 and POW1 were not included in the statistical analysis due to a low number of eyes with reliable measurements.

Statistical analysis

All analyses were conducted using STATA V.14.0/IC (StataCorp, College Station, TX). The sample size was chosen to achieve a statistical power of 80% for the group comparison at a 5% significance level. Wilcoxon signed-rank test and paired t-test were used to compare the outcomes between the two techniques, as appropriate. Bivariate correlations were assessed using Spearman's correlation coefficient (r), except for the correlation between CCT and BSS use in the FLACS group, which was assessed using Pearson's correlation coefficient (r). A p value <0.05 was considered statistically significant.

RESULTS

A total of 154 eyes of 77 patients met our inclusion criteria, and thus were recruited into the study. However, 10 patients were later excluded. Of those, two patients had CPS in both eyes (inability to perform FLACS due to anatomical features) and another two had FLACS in both eyes (due to patient's preference after having FLACS in the first eye). Six patients missed their 3 months' follow-up visit. Therefore, 134 eyes of 67 patients were analysed in this study. The mean age of patients was 68.3 ± 9.1 years (range 33–88 years). Over half (56.7%) of the study population were females.

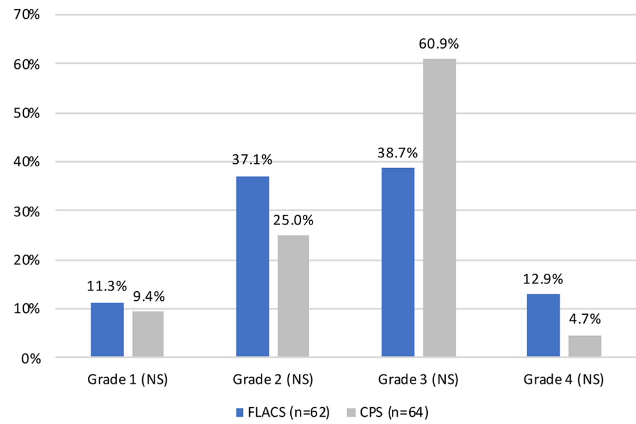

Figure 1 Percentage of eyes with different types of nuclear sclerosis according to the Lens Opacities Classification System III (LOCS III) grading system between the two groups. CPS, conventional phacoemulsification surgery; FLACS, femtosecond laser-assisted cataract surgery; NS, nuclear sclerosis.

Preoperatively, there was no statistically significant difference in NS grade between the two groups (p=0.7). Figure 1 shows the percentage of eyes with different types of NS according to the LOCS III grading system between the two groups.

Intraoperatively, BSS use, irrigation/aspiration time for cortex removal and OR time were significantly higher in the FLACS group (p<0.001) (table 2). However, CDE and EPT were similar between the two groups. Of note, one case of intraoperative posterior capsular block syndrome (PCBS) was encountered in the FLACS group, necessitating anterior vitrectomy and sulcus IOL placement.

Preoperative and postoperative ECD values were not significantly different between FLACS and CPS groups (table 3). Likewise, the difference in ECL was not statistically significant between the two groups at POM1 or at POM3.

Preoperative CCT was not significantly different between the two groups (table 4). Also, no significant difference was observed in CCT between the two groups over the follow-up period. While the mean relative change in CCT was higher in the CPS group, the difference was not statistically significant at POM1 and POM3.

Table 5 shows correlations between postoperative outcomes and each of the preoperative and intraoperative parameters. In the FLACS group, each of NS grade, BSS use, CDE and EPT were negatively correlated with ECD at POM3. A positive, statistically significant correlation was noted between CCT and each of CDE, BSS use and EPT at POM3. In the CPS group, the CDE was negatively correlated with ECD at POM3. None of the other examined parameters were significantly correlated with ECD or CCT. CDE correlated with the NS grade in both FLACS and CPS groups (r=0.37 with p=0.007 and r=0.48 with p<0.001, respectively).

Table 2 Means (±SDs) of intraoperative parameters in the FLACS and CPS groups

Parameter	FLACS group	CPS group	P value*
CDE	6.7±4.5	6.9±5.3	0.84
EPT (s)	0.6±0.3	0.6±0.3	0.70
BSS use (mL)	67.0±17.6	55.4±13.6	**<0.001**
Irrigation/aspiration time for cortex removal (s)	83.5±37.8	49.3±32.8	**<0.001**
OR time (min)	8.0±2.8	6.6±1.9	**<0.001**

Bold values indicate significance. Means (+/- SDs) of intraoperative parameteres in the FLACS and CPS groups.
*Wilcoxon signed-rank test.
BSS, balanced salt solution; CDE, cumulative dissipated energy; CPS, conventional phacoemulsification surgery; EPT, effective phacoemulsification time; FLACS, femtosecond laser-assisted cataract surgery; OR, operating room.

Table 3 Mean (±SD) corneal endothelial cell density (cells/mm^2) and percentage of endothelial cell loss (%) between the FLACS and CPS groups at each follow-up point

	ECD (cells/mm^2)			ECL (%)		
Exam	FLACS group	CPS group	P value*	FLACS group	CPS group	P value*
Preoperative	2645±275	2644±309	0.37			
POM1	2370±580	2467±564	0.18	10.7±20.0	6.8±18.0	0.18
POM3	2374±527	2433±526	0.19	11.2±17.9	8.0±18.5	0.10

*Wilcoxon signed-rank test.
CPS, conventional phacoemulsification surgery; ECD, endothelial cell density; ECL, endothelial cell loss; FLACS, femtosecond laser-assisted cataract surgery; POM1, postoperative month 1; POM3, postoperative month 3.

DISCUSSION

Endothelial cells play a pivotal role in the maintenance of corneal transparency. ECL can predispose to the development of corneal oedema, and thus the loss of corneal transparency. While endothelial attrition occurs naturally with time, insults to the corneal endothelium (eg, surgery) can accelerate this process. Several factors may make the endothelium susceptible to injury during surgery, such as patient age, cataract density and anterior chamber depth.[14 15 19] Intraoperatively, irreversible injury may occur due to excessive manipulation, use of ultrasound (US) energy, ricocheting of nuclear fragments, fluid turbulence during irrigation/aspiration and IOL or surgical instrument contact with the cornea.[20–24] With the introduction of FL to cataract surgery, the debate about whether FLACS affects the rate of ECL differently than CPS has continued, with several limitations in the existing literature.[17]

It was reported that reduction of US energy consumption could lead to a decrease in the postoperative corneal ECL.[25] With CPS, the ECL rate has been reported to be around 4%–25%.[20] However, it may be greater in eyes with hard nuclei, reaching as

Table 4 Central corneal thickness (µm) and mean relative change in central corneal thickness (%) between the FLACS and CPS groups at each follow-up point (mean±SD)

	CCT (µm)			Mean relative change in CCT (%)		
Exam	FLACS group	CPS group	P value	FLACS group	CPS group	P value
Preoperative	581±45	579±49	0.59			
POD1	607±59	574±45	0.08	8.4±9.1	3.9±8.0	0.25
POW1	595±63	604±57	0.29	3.7±8.0	6.9±8.2	0.10
POM1	593±50	590±57	0.27*	2.4±8.4	3.0±9.2	0.84*
POM3	578±52	578±48	0.99	0.2±5.8	0.8±7.1	0.63

*Wilcoxon signed-rank test.
CCT, central corneal thickness; CPS, conventional phacoemulsification surgery; FLACS, femtosecond laser-assisted cataract surgery; POD1, postoperative day 1; POM1, postoperative month 1; POM3, postoperative month 3; POW1, postoperative week 1.

Table 5 Correlation coefficients (r) for intraoperative and postoperative outcomes

	FLACS group	P value	CPS group	P value
CDE and NS	0.37	**0.007**	0.48	**<0.001**
ECD (POM3) and:				
NS	−0.15	0.26	−0.11	0.40
BSS use	−0.33	0.02	−0.04	0.80
CDE	−0.26	0.07	−0.34	0.01
EPT	−0.28	0.06	−0.04	0.80
CCT (POM3) and:				
CDE	0.41	0.03	0.1	0.61
BSS use*	0.49	0.007	0.06	0.75
EPT	0.38	0.04	−0.18	0.37

Bold values indicate significance.
*Pearson's correlation.
BSS, balanced salt solution; CCT, central corneal thickness; CDE, cumulative dissipated energy; CPS, conventional phacoemulsification surgery; ECD, endothelial cell density; EPT, effective phacoemulsification time; FLACS, femtosecond laser-assisted cataract surgery; NS, nuclear sclerosis; POM3, postoperative month 3.

high as 42% 2 months after surgery.[26] Previous studies showed a reduction in US energy, EPT and CDE with FL pretreatment.[8–12] In our study, we found no statistically significant difference in ECL between the two groups. This is in contrast with the findings observed in another intraindividual randomised clinical trial, which showed a significantly lower ECL in the FLACS group compared with CPS group.[27] Despite the matching study design, three observed differences should be noted between this study and the previously published one by Conrad-Hengerer *et al*.[27] First, they observed a lower use of US energy in the FLACS group (mean EPT 0.0±0.1 s) compared with CPS group (mean EPT 1.4±0.1 s), whereas mean EPT was the same (0.6±0.3 s) in both groups in this study. Second, the amount of irrigation fluid used in their study was higher than in our study (91±12 mL in FLACS and 89±10 mL in CPS group vs 67±17.6 mL and 55.4±13.6 mL in our study). Third, corneal incisions were made manually for the FLACS group in their study but using FL in this study. Although a combination of these factors may account for the differences in observed findings, we suspect that the creation of corneal incisions using FL could potentially be the most contributing factor.

Indeed, previous studies suggested that the addition of laser-automated corneal incisions to FLACS could lead to greater ECL postoperatively than with manually created incisions.[28] In addition, several previous reports in which incisions were created using FL found no significant difference in endothelial cell counts between the two groups (similar to our study),[29 30] while other studies with manual incisions found a significant difference in ECL, favouring FLACS over CPS.[10 27 31]

Comparing the FLACS with CPS groups in our study, we did not observe a significant difference in postoperative CCT at any time point during the follow-up period. Since we observed no significant difference in ECD values between the two groups, it was expected that CCT would be similar between the two groups. It is interesting to note that even in studies that have reported reduced energy use in FLACS versus CPS, there was no difference in CCT at POM1.[29 31]

Previous studies recommended the use of FLACS in high-risk cases such as guttae or Fuchs' dystrophy because of the anticipated protection against postoperative ECL. However, our study findings do not support such a recommendation. While patients with Fuchs' dystrophy may exhibit a postoperative response that is different from healthy eyes, emerging evidence suggests that CCT[32] and corneal decompensation[33] are similar between FLACS and CPS in eyes with compromised endothelial function (eg, Fuchs' dystrophy).

Finally, the mean time for irrigation/aspiration of the cortical material was significantly higher in the FLACS group with an overall higher OR time (table 2). In a previous intraindividual study, significantly higher OR time was observed in the FLACS group in comparison with CPS.[34] Such time difference was hypothesised to be due to learning curve. In our study, this was not the case. It is interesting to note that irrigation/aspiration step was, on average, 30 s longer in the FLACS group compared with the CPS group. We assume that the reason for this is more adherent cortical material in such eyes due to the thermal effect caused by the FL.[35] In terms of intraoperative complications, we encountered one case of PCBS in the FLACS group. It should be noted that the final outcomes, in terms of ECD and pachymetry, were comparable to the outcomes observed in the rest of the study population.

While the rigour of this study's design is duly acknowledged, there are a few limitations to be considered. According to the literature, endothelial cell recovery after cell damage may take up to 6 months.[15] Therefore, further studies with longer follow-up will likely be needed to fully evaluate the effect of FL in the corneal ECD during cataract surgery. In addition, it is well known that specular microscope measures a small area of the cornea, which might not be truly representative of the total corneal endothelial cell population.

In conclusion, changes in ECD and CCT did not differ significantly between the FLACS and CPS groups over a 3-month follow-up period. We hypothesise that the creation of corneal incisions by the FL might be implicated in an additional injury to endothelial cells, resulting in an overall ECL rate that is similar to that in CPS. Further studies, designed specifically to investigate whether avoiding FL-assisted corneal incisions could provide extra endothelial cell protection, are strongly encouraged.

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