Femtosecond laser-assisted cataract surgery compared with phacoemulsification: the FACT non-inferiority RCT

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Declared competing interests of authors: none

Published January 2021
DOI: 10.3310/hta25060

Scientific summary

The FACT non-inferiority RCT

Health Technology Assessment 2021; Vol. 25: No. 6
DOI: 10.3310/hta25060

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Cataract surgery is one of the most commonly performed operations in the Western world, with almost half a million of these operations performed per year in the UK alone. The current standard method, phacoemulsification cataract surgery (PCS) (using ultrasound), was introduced > 50 years ago. An alternative, femtosecond laser-assisted cataract surgery (FLACS), first became commercially available almost 10 years ago. The reported advantages of FLACS include more accurate positioning, more reproducible shape and size of the capsulotomy when compared with a capsulorrhexis, and less intraocular lens tilt with fewer higher-order aberrations. In addition, by using a laser to fragment the crystalline lens, less ultrasound energy is subsequently required to complete its removal, which should result in less endothelial cell loss. Overall, this would be expected to translate to greater safety and better visual outcomes through greater precision and reproducibility.

When they were introduced, laser cataract surgery platforms were marketed as bringing a stepwise improvement in surgical technique and were used as a differentiating factor between cataract surgery providers. The cost of FLACS remains high, which reflects the high development costs. For example, Alcon (Geneva, Switzerland) took over LenSx for US$744M in 2010 and Abbott Medical Optics (Abbott Park, IL, USA) purchased OptiMedica Corp. for up to US$400M in 2013. To date, there are limited high-quality data from randomised controlled trials on outcomes from laser cataract surgery compared with outcomes from the standard technique, with the data that are available being predominantly from large comparative case series. The 2016 Cochrane review of FLACS compared with PCS concluded that there was limited evidence to determine the equivalence or superiority of FLACS, and that large, adequately powered randomised controlled trials were needed (Day AC, Gore DM, Bunce C, Evans JR. Laser-assisted cataract surgery versus standard ultrasound phacoemulsification cataract surgery. *Cochrane Database Syst Rev* 2016;**7**:CD010735). Three meta-analyses have been published; (Chen X, Xiao W, Ye S, Chen W, Liu Y. Efficacy and safety of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract: a meta-analysis of randomized controlled trials. *Sci Rep* 2015;**5**:13123; Popovic M, Campos-Möller X, Schlenker MB, Ahmed II. Efficacy and safety of femtosecond laser-assisted cataract surgery compared with manual cataract surgery: a meta-analysis of 14 567 eyes. *Ophthalmology* 2016;**123**:2113–26; and Ye Z, Li Z, He S. A meta-analysis comparing postoperative complications and outcomes of femtosecond laser-assisted cataract surgery versus conventional phacoemulsification for cataract. *J Ophthalmol* 2017;**2017**:3849152) one found superior refractive outcomes for FLACS, whereas the others found no statistically significant differences in terms of patient-reported visual, refractive and complications. Two large randomised controlled trials have recently been published: the French FEMCAT (FEMtosecond laser-assisted versus phacoemulsification CATaract surgery) trial, which found no difference in visual or safety measures between FLACS and PCS [Schweitzer C, Brezin A, Cochener B, Monnet D, Germain C, Roseng S, *et al.* Femtosecond laser-assisted versus phacoemulsification cataract surgery (FEMCAT): a multicentre participant-masked randomised superiority and cost-effectiveness trial. *Lancet* 2020;**395**:212–24], and a UK trial from St Thomas' Hospital of 400 eyes (Roberts HW, Wagh VK, Sullivan DL, Hidzheva P, Detesan DI, Heemraz BS, *et al.* A randomized controlled trial comparing femtosecond laser-assisted cataract surgery versus conventional phacoemulsification surgery. *J Cataract Refract Surg* 2019;**45**:11–20) found similar visual outcomes between its arms and a statistically significantly lower posterior capsule tear rate in the FLACS arm.

Objective

The aim of this trial, FACT (Femtosecond laser-Assisted Cataract Trial), is to establish whether FLACS is a cataract surgical technique that is as good as or better than PCS.

Primary outcome

The primary outcome was uncorrected distance visual acuity [measured using a ETDRS (Early Treatment Diabetic Retinopathy Study) logMAR (logarithm of the minimum angle of resolution) chart at a starting distance of 4 m] in the study eye at the 3-month follow-up.

Secondary outcomes

Secondary outcomes were corrected distance visual acuity at 3 months in the study eye, safety measures including intraoperative and postoperative complications and corneal endothelial cell count change and refractive error (spherical equivalent) within 0.5 dioptre and within 1.0 dioptre of intended refractive outcomes. Health-related quality of life was measured at 6 weeks and 3, 6 and 12 months using the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), questionnaire plus the vision bolt-on question and patient-reported vision health status using Catquest-9SF (a Rasch-validated instrument). All trial follow-ups were performed by optometrists who were masked to the trial intervention.

Methods

We designed a pragmatic, randomised controlled non-inferiority trial with participants who were unmasked to treatment allocation across three NHS sites, to compare FLACS with PCS.

All patients were screened and recruited from routine cataract clinics. They were adults aged $\geq$ 18 years with age-related cataract. For a patient to be eligible for participation, the expected postoperative refractive target had to be within $\pm$ 0.5 dioptre of emmetropia (i.e. good distance vision).

Randomisation was carried out using minimisation with a random element, and with treatment centre, surgeon and the number of eyes that as stratification factors. Participants were randomised 1 : 1 to undergo either FLACS or PCS. A secure online service (Sealed Envelope™, Sealed Envelope Ltd, London, UK; www.sealedenvelope.com) provided computer-generated participant identifiers and the trial arm allocations. For participants who required bilateral cataract surgery, the same intervention (namely FLACS or PCS) was offered when the patient returned for their second eye surgery, unless the patient wished otherwise. Owing to the nature of the intervention, surgeon and participant masking was not possible. All trial follow-ups were performed by optometrists who were masked to the trial intervention.

Follow-up

Participants attended a follow-up visit at 3 months post study eye surgery and again at 12 months.

Outcome measures

The primary outcome was uncorrected distance visual acuity (logMAR) at 3 months following surgery on the study eye, measured using a standard ETDRS chart at a starting distance of 4 m. Additional secondary outcome measures included visual acuity outcomes, refractive outcomes, adverse events, health-related quality of life and resource use.

Sample size

We aimed to recruit at least 808 patients (404 per arm). This sample size was estimated to to allow the identification of a treatment effect size of 1 logMAR line uncorrected distance visual acuity, which we thought would be clinically important to patients and ophthalmologists as determined by prior patient and public involvement in the trial design. One logMAR line is 5 letters (each letter is 0.02 logMAR) and the test–retest variability is reported to be about 0.07 logMAR on letter-by-letter scoring. If there is

truly no difference in mean logMAR between the two treatment arms, then 432 patients (216 per arm) would provide 90% power to be sure that a 95% two-sided confidence interval would exclude the non-inferiority limit of 0.1 logMAR, assuming a common standard deviation of 0.32. The standard deviation is from the Royal College of Ophthalmologists' National Ophthalmic Database uncorrected distance visual acuity data.

As patients were clustered within operating surgeons, each patient could not be assumed to generate independent information. To take account of this, the sample size was increased by an inflation factor of 1.59, giving a required sample size of 688 patients (344 per arm). To allow for an anticipated 15% dropout rate (the median age of patients undergoing cataract surgery in the UK is 77 years and many of these patients have significant systemic comorbidities), the total sample size required was 808 patients.

Statistical methods

As detailed in the statistical analysis plan (excluding the health economic evaluation) that was approved before the analyses were carried out, missing outcome data for the primary outcome were imputed using only multiple imputation with chained equations, and the results were combined using Rubin's rules. All secondary outcome analyses were performed on complete cases only. All analysis models included information on the site and on the number of eyes that were eligible as covariates; details about the surgeon were included in the analysis models as random effects. The model for the primary outcome was also adjusted for baseline habitual logMAR visual acuity values, and similar adjustments were made for any continuous secondary outcomes if a baseline value was recorded. Astigmatism at baseline [as measured by keratometry readings from Pentacam® (OCULUS Optikgeräte GmbH, Wetzlar, Germany) corneal topography] was incorporated as an adjustment factor in the analyses of visual acuity outcomes. Adjusted treatment effect estimates, two-sided 95% confidence intervals and two-sided *p*-values were reported for each outcome measure. Further supportive analyses of the primary outcome were carried out, including a per-protocol analysis and complete-case analysis.

Economic evaluation

The aim of the economic evaluation was to conduct a within-trial analysis of the mean incremental cost per quality-adjusted life-year gained by FLACS compared with PCS over 12 months from a health and social care cost perspective. A secondary analysis from a societal cost perspective was also conducted. Given that the primary outcome of the trial was uncorrected distance visual acuity at 3 months, a cost-effectiveness analysis was also conducted for 3 months. Multiple imputation by chained equations and bootstrapping were used to construct cost-effectiveness acceptability curves and cost-effectiveness planes.

Results

Between May 2015 and September 2017, a total of 3448 patients were assessed for eligibility (1710 were excluded because they were ineligible). Of the 1738 patients who were eligible, we recruited 785, of whom 392 were randomly assigned to the FLACS arm and 393 were randomly assigned to the PCS arm. The average age of the patients was 68 years (± 10 years), and more female than male patients were recruited (52% female, 48% male). In total, 70% of all participants were of white ethnicity (black/black British was the second largest ethnic group at 14%). A total of 20% of the participants had undergone previous cataract surgery in one eye. The baseline characteristics of participants were similar in both treatment arms.

A total of 352 out of 392 (90%) participants who were allocated to the FLACS arm and 317 out of 393 (81%) participants who were allocated to the PCS arm attended their follow-up visit 3 months postoperatively. The mean uncorrected distance visual acuity difference between the treatment arms was −0.01 logMAR (95% confidence interval −0.05 to 0.03 logMAR) and the mean corrected distance visual acuity difference was −0.01 logMAR (95% confidence interval −0.05 to 0.02 logMAR). Seventy-one per cent of FLACS and 70% of PCS cases were within ± 0.5 dioptre of the reflective target, and 93% of

FLACS cases and 95% of PCS cases were within ± 1.0 dioptre. There were two posterior capsule tears in the PCS arm and none in the FLACS arm.

A total of 311 out of 392 (79%) participants who were allocated to the FLACS arm and 292 out of 393 (74%) participants who were allocated to the PCS arm attended their follow-up visit at 12 months. The mean uncorrected distance visual acuity difference between treatment arms was –0.03 logMAR (95% confidence interval –0.06 to 0.01 logMAR) and the mean corrected distance visual acuity difference was –0.03 logMAR (95% confidence interval –0.06 to 0.01 logMAR). Seventy-five per cent of both FLACS and PCS cases were within ± 0.5 dioptre refractive target, and 95% of FLACS and 96% of PCS cases were within ± 1.0 dioptre. There were no significant differences between the treatment arms for any other outcome, with the exception of mean binocular corrected distance visual acuity difference of –0.02 logMAR (95% confidence interval –0.05 to 0.00 logMAR; $p = 0.036$) favouring the FLACS arm.

In the FLACS arm, surgery took a mean time of 17.1 minutes (standard deviation 7.4 minutes). The FLACS laser procedure took an additional 3.9 minutes (standard deviation 3.5 minutes), with a total time of 20.8 minutes (standard deviation 8.2 minutes). In the PCS arm, surgery took 17.8 minutes (standard deviation 8.0 minutes). There was no significant difference in the use of anaesthetic drugs or consumables between treatment arms except for VisionBlue® [D.O.R.C. (Dutch Ophthalmic Research Center) (International) B.V., Zuidland, the Netherlands; used for staining the anterior capsule to increase visibility in 43 patients in the PCS arm and in three patients in the FLACS arm] at a cost of £8.65 per vial.

There were no significant differences between the two treatment arms for any health, social care or societal costs. For the economic evaluation, the mean cost difference (FLACS minus conventional phacoemulsification) for the imputed, bootstrapped, adjusted data was £167.62 per patient (95% of iterations between –£14.12 and £341.67). The mean QALY difference (FLACS minus PCS) was 0.001 (95% of iterations between –0.011 and 0.015). This equates to an incremental cost-effectiveness ratio (cost difference divided by QALY difference) of £167,620.

For the threshold analysis from a health and social care cost perspective, assuming that FLACS results in an additional 0.001 QALYs per patient, FLACS needs to cost £138 less than it currently does to potentially be cost-effective at a willingness-to-pay threshold of £30,000 for a QALY gained.

Conclusions

In terms of vision FLACS is not inferior to PCS. There were no clinically important differences in patient-reported health and safety outcomes after 12 months' follow-up. A difference was found for binocular corrected distance visual acuity, which, although statistically significant, was not clinically significant. FLACS was not found to be cost-effective.

Implications for health care

Both FLACS and PCS have similar visual, refractive and safety outcome measures. FLACS is a more expensive technique than PCS and is not cost-effective in its present form.

Recommendations for research

It is possible that FLACS may offer advantages over PCS for patients with certain subtypes of cataract, or for lens replacement surgery using multifocal or other 'premium' intraocular lens, but further research may be required.

Trial registration

This trial is registered as ISRCTN77602616.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 6. See the NIHR Journals Library website for further project information. Moorfields Eye Charity (grant references GR000233 and GR000449 for the endothelial cell counter and femtosecond laser used).

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/04/46. The contractual start date was in September 2014. The draft report began editorial review in January 2020 and was accepted for publication in July 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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