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Benefits and Harms of Femtosecond Laser Assisted Cataract Surgery: A Systematic Review

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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EXECUTIVE SUMMARY

BACKGROUND

The preferred method of removing cataracts in the developed world is phacoemulsification. Using this technique, ultrasonic energy softens the dense lens material of the cataract, which is then extracted from the eye with suction and irrigation. Current practice includes creating manual corneal incisions and anterior capsulotomies, followed by phacoemulsification. Recently these three manual procedures have been performed in an automated fashion with the use of the femtosecond laser (FSL). Several FSL systems have been approved by the FDA for use in the U.S. for some or all of these procedural steps in cataract surgery. FSL technology has been widely used in various refractive surgery applications in recent years. Studies have suggested decreased phacoemulsification energy use with FSL cataract surgery and have examined the potential advantages of more precise corneal incisions and capsulotomy formation.

Cataract surgery is a frequently performed operation in the VHA, with more than 49,000 performed in 2012. As a result, the VHA National Surgery Office has been tasked with making a recommendation regarding whether femtosecond lasers provide appropriate cost-benefit and risk-benefit ratios to support implementation for cataract surgery in the VA. The purpose of this systematic review is to examine the effectiveness and safety of femtosecond laser assisted cataract surgery (FLACS) relative to conventional cataract surgery. Key questions were developed in conjunction with the stakeholders which address the effectiveness, safety, adverse consequences and economic implications of adopting FLACS into the VA system.

METHODS

We conducted a primary review of the literature by systematically searching, reviewing and analyzing the scientific evidence as it pertains to the research questions. To identify relevant articles, we began by searching MEDLINE®, CINAHL and the Cochrane Database of Systematic Reviews. We further evaluated the bibliographies of included primary studies and any systematic or nonsystematic reviews that were identified. To identify in-progress or unpublished studies, we searched ClinicalTrials.gov. We also searched conference proceedings of ophthalmologic societies and topic specific journals, including the following: The American Society of Cataract and Refractive Surgery; Journal of Cataract & Refractive Surgery; American Academy of Ophthalmology; Ophthalmology; International Society of Refractive Surgery; American Academy of Ophthalmic Executives; The Foundation of the American Academy of Ophthalmology, The Royal College of Ophthalmologists; COS Conference Papers Index; and Proceedings First (OCLC).

Two reviewers trained in the critical analysis of literature assessed for relevance the abstracts of citations identified from literature searches. Two reviewers independently assessed full-text articles for inclusion; disagreements were resolved through consensus. We assessed the quality of each study using published tools. We assessed the overall quality of the body of evidence for each outcome using a method developed by the Grades of Recommendation, Assessment,

Development and Evaluation (GRADE) Working Group. We critically analyzed the evidence on effectiveness and adverse effects and compiled a narrative synthesis of findings. We conducted meta-analyses of two commonly reported outcomes in FSL and conventional cataract surgery procedures, corrected distance visual acuity (CDVA) and effective phacoemulsification time (EPT).

RESULTS

We reviewed 468 titles and abstracts from the electronic search and identified 436 additional references through manual searching of reference lists, input from technical advisors and reviewing conference proceedings of ophthamalogic societies for recent unpublished or ongoing studies.

After applying inclusion/exclusion criteria at the abstract level, seventy full-text articles were reviewed, as shown in Figure 2. Of the full-text articles, we rejected fifty-four that did not meet our inclusion criteria.

Key Question 1: What is the evidence that FLACS is associated with better outcomes than conventional cataract surgery?

We identified nine studies addressing the comparative effectiveness of FLACS versus conventional surgery, including three small to medium-sized randomized controlled trials. Six of these studies (and all three of the randomized controlled trials) were conducted at Semmelweis University, Budapest, Hungary, all surgeries having been performed by the same surgeon, using the Alcon LenSx laser. Two studies were conducted in an ophthalmology group practice, at Launceton Eye Hospital, Tasmania, Australia, using the OptiMedica Catalys laser. Sample sizes in these studies ranged from 25 to 400 patients, with follow-up periods extending from two weeks to one year.

The most commonly reported relevant outcomes in these comparative studies were: post-operative corrected distance visual acuity (CDVA) and effective phacoemulsification time (EPT). We conducted a meta-analysis of CDVA and EPT, but heterogeneity precluded calculation of a reliable summary effect estimate. The results of individual studies are presented in Figures 3 and 4. Overall, there was low evidence of benefit from three randomized controlled trials and six observational studies. There were no significant differences noted between groups for CDVA outcomes. EPT outcomes were mixed, with results either comparable between FSL and conventional cataract surgery groups or favoring FSL groups. No studies addressed quality of life measures. Methodological concerns were noted regarding the generalizability of studies conducted from limited sites and potential sample selection bias from enrollment into FSL and conventional surgery groups.

Key Question 2a: What are the adverse effects that have been reported for FLACS?

Seven studies were identified addressing adverse effects, unique to FLACS. Sample sizes in these studies ranged from 25 to 1300 patients, with follow-up periods extending from immediately following the procedure, to three months post-operative.

We grouped the adverse event outcomes in these studies by either: 1) those occurring as a result of difficulties with the laser-patient interface, or 2) the change in intraocular pressure (IOP) measured during the FLACS procedure. Five studies reported difficulties related to the laser interface with the ocular surface (including the orbital structures). Two studies measured intraocular pressure (IOP) fluctuation during FLACS procedures. A small proportion of patients experienced suction breaks, second docking attempts and aborted procedure adverse events. FSL application is also associated with an increase in IOP. Overall, we found moderate to low strength of evidence for adverse events with methodological concerns raised from enrollment criteria used for FSL surgery groups.

Key Question 2b: What is the risk of adverse effects from FLACS compared to the risk associated with conventional cataract surgery?

Nine studies addressed the adverse effects of FLACS compared to conventional cataract surgery. Sample sizes in these studies ranged from 25 to 400 patients, with follow-up periods extending from one week to one year.

We grouped the adverse event outcomes of these studies by the ocular structures which were affected. Five of these studies reported, variously: capsulotomy configuration, position and the resultant effects on IOL decentration and refractive outcomes. Two of these studies reported post-operative corneal edema by measuring either corneal thickness or corneal endothelial cell loss. An additional two studies compared post-operative macular thickness and morphology, as measured by optical coherence tomography (OCT). The FSL and control groups were similar for post-operative corneal thickness and macular edema measurements, with corneal endothelial cell loss decreased in the FSL group in one study. Overall, we found moderate to low strength of evidence for comparative adverse events with methodological concerns from enrollment criteria used for the FSL and conventional surgery groups.

Key Question 3: What is the evidence that the experience of the surgeon is associated with adverse effects of FLACS?

Three studies reported outcomes relevant to the experience of the surgeon in performing the FLACS procedure. Sample sizes in these studies ranged from 200 to 1300 patients, with follow-up periods extending from two weeks to three months. Overall, one of the studies found no significant differences between outcomes for initial and subsequent groups of patients undergoing FLACS, while on the other hand, two studies from the same team of researchers found significantly fewer complications associated with greater experience with FLACS.

There were methodological concerns from enrollment criteria used for the FSL and conventional surgery groups.

DISCUSSION

We found no evidence that FLACS differs from conventional cataract surgery on measures of safety and effectiveness. The unique risks associated with FLACs are primarily related to laser docking interface difficulties, which may be reduced with increasing surgical experience with the procedure. The comparative adverse event risks of FLACS and conventional surgery were

similar. Complications rates in FLACS cohorts were found to be reduced or unchanged by surgical experience in the included studies of this review.

We found moderate evidence of comparable CDVA outcomes between FLACS and conventional cataract surgery groups. We noted limited evidence for a reduction of EPT in the FSL compared to the conventional cataract surgery group. Furthermore, meta-analyses found no statistically significant differences between FSL and conventional groups in either CDVA or EPT. No studies reported findings related to quality of life outcomes or cost effectiveness of FLACS relative to conventional cataract surgery.

Most of the included studies reported on the comparative risks of adverse effects between FSL and conventional cataract surgery. Reports of adverse events were similar between FSL and conventional groups, including IOL positioning, corneal thickness, macular edema and residual refractive error. The association between the experience of the surgeon and FLACS adverse effects was limited to three eligible studies, two of which were conducted by the same team of researchers. These studies reported mixed results of surgical experience reducing the incidence of FLACS adverse events.

There were methodological concerns for the included studies that represent potential sources of bias that threaten the validity of study findings. Many studies had small to medium sample sizes. Study methods were often unclear, particularly with regard to the application of inclusion and exclusion criteria for FSL treatment groups and the enrollment of treatment and control cohorts. Studies often excluded patients with denser cataracts, comorbidities and those deemed uncooperative from the FSL treatment groups. In addition, many study protocols centered around patients self-selecting into FSL or conventional surgery groups.

The majority of included studies (all but two) report financial conflicts of interest, with included studies clustered around a limited number of geographic sites, conducted by the same team of coauthors. All four of the included randomized trials were conducted by the same research group and every surgery (FSL or conventional) was completed by the same surgeon, who was also a study co-author. It is also unclear whether or not there was any overlap in the study patient populations of these trials, given they are conducted at the same site and at what appeared to be a similar timeframe.

CONCLUSION

This systematic review found visual outcomes (CDVA) and EPT to be similar in FLACS and conventional surgery, while quality of life and cost-effectiveness outcomes were not reported. The evidence for the relative benefit of FLACS was limited by reliance on small to moderately-sized prospective cohort studies, nearly all of which had stated financial conflicts of interest. Adverse events unique to FLACS involved difficulties in laser docking or patient suitability for the procedure. Many patients were excluded from the FSL treatment groups for orbital, corneal, cataract density, or medical co-morbidities. Comparative adverse events in FLACS and conventional surgery were found to be similar for IOL positioning, corneal thickness, macular edema and residual refractive error. A few studies reported mixed results of the effect of surgical experience on the incidence of FLACS adverse events.

Summary of the evidence table on the effects of femtosecond laser assisted cataract surgery

Outcome	For each study design: Number of studies (combined sample size)	Findings	Strength of Evidence	Comments
Visual acuity	2 RCTs (N=189) 4 NRCS (N=306)	No significant differences	Low	No differences in visual acuity outcomes found in either of the randomized trials. Unclear risk of bias for trials, low consistency, coherence and applicability of estimated effects across studies, small to medium sample sizes and conflicts of interest lower the strength of evidence.
Effective phacoemulsi-fication time	1 RCT (N=76) 4 NRCS (N=615) 1 NCS (N=160)	Mixed findings	Low	Trial found no significant reduction in EPT for FSL group. Two of the large nonrandomized studies (N=550) reported significant reductions in favor of FLACS. Remaining three studies found no significant differences. Unclear risk of bias for trial, low consistency, coherence and applicability of estimated effects across studies and conflicts of interest lower the strength of evidence.
Quality of life	None	None	No evidence	None of the included studies reported on quality of life outcomes.
Intraoperative complications*	3 NRCS (N=1,900) 3 NCS (N=285)	Higher IOP for FLACS; Few additional complications for FLACS	Moderate to Low	Low incidence of complications with FLACS, though increases in IOP reported across studies. Low applicability of estimated effects lowers the strength of evidence.
Postoperative complications**	1 RCT (N=76) 1 NRCS (N=150) 1 NCS (N=160)	Mixed findings	Low	Trial found no significant differences and medium-sized cohort study (N=150) found significantly reduced endothelial loss for the FLACS group. Unclear risk of bias for trial, low consistency and coherence of estimated effects across studies, small to medium sample sizes and conflicts of interest lower the strength of evidence.
Costs	None	None	No evidence	None of the included studies reported on costs of FLACS compared to conventional cataract surgery.

Abbreviations: RCT = randomized controlled trial; NRCS = non-randomized comparative studies; NCS = non-comparative studies; FLACS = femtosecond laser assisted cataract surgery; EPT = effective phacoemulsification time; IOP = intraocular pressure

*Intraoperative complications include: capsular blockage, capsular tear, dislocated nucleus, docking failure

**Postoperative complications include: infection, retinal swelling/cystoid macular edema, intraocular decentration, corneal edema