Comparison of clinical outcomes between 'on-flap' and 'off-flap' epi-LASIK for myopia: a meta-analysis
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CRD summary
The review concluded that off-flap and on-flap epipolis laser in situ keratomileusis (epi-LASIK) had equal visual and refractive outcomes for the treatment of myopia but off-flap epi-LASIK had significantly faster epithelial healing and visual recovery than on-flap epi-LASIK. Due to study variability and small study size, the conclusions should be interpreted with caution.

Authors' objectives
To compare the efficacy and safety of on-flap epipolis laser in situ keratomileusis (Epi-LASIK) versus off-flap epi-LASIK for myopia.

Searching
PubMed, EMBASE, Chinese Biological Medicine and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to March 2011 with no language restrictions; search terms were reported. Relevant articles and reviews were handsearched. Google and Yahoo were also searched for relevant information. Only published clinical trials were included; letters, review articles and conference abstracts were excluded.

Study selection
Eligible randomised controlled trials (RCTs) and non-randomised comparative studies compared on-flap epipolis laser in situ keratomileusis (epi-LASIK) versus off-flap epi-LASIK for correcting myopia. Patients had to be 18 to 60 years old, have any degree of myopia and of up to three diopters (D) of astigmatism, no significant co-pathology, no history of previous ocular surgery and no systemic disease associated with impaired or abnormal wound healing. At least one relevant outcome had to be considered such as: visual and refractive outcomes for at least three months post-treatment; loss of at least one line of best spectacle-corrected visual acuity at least three months post-treatment; mean time of epithelial healing; pain scores at day one after treatment; and corneal haze scores at six and 12 months after treatment.

Most studies were in Asia with one in Greece. Two studies included two groups of patients. Mitomycin C (0.02%) was used for a range of 15 second to two minutes in 67% studies. The mean age of patients ranged from 20.25 to 33 years; where reported, the number of males ranged from 16% to 61%. Mean pre-operative manifest spherical equivalent ranged from -3.49D to -9.14D. Corneal haze scores ranged from 0 to 4 and definitions were provided.

The authors did not report how many reviewers performed the study selection.

Assessment of study quality
Two independent reviewers performed the quality assessment, with any discrepancies resolved by discussion. The Jadad score/scale was used to assess quality, giving a score out of five for five criteria including randomisation, blinding, withdrawals and dropouts.

Data extraction
Two independent reviewers performed the data extraction, with any discrepancies resolved by discussion. The numbers of events were used to calculate odds ratios (OR) with 95% confidence intervals (CI). For continuous data, means and standard deviations were used to calculate mean differences with 95% CI.

Methods of synthesis
Results were pooled using a fixed-effects model if there was no significant heterogeneity and a random-effects model if there was significant clinical diversity or heterogeneity (DerSimonian-Laird) to give weighted mean differences (WMDs) with 95% confidence intervals and odds ratios with 95% confidence intervals. Study heterogeneity was assessed using $I^2$ and $X^2$; values of $I^2$ over 50% indicated significant heterogeneity. Publication bias was assessed visually using funnel plots. Sensitivity analyses were performed to find the effect of study design.
Results of the review
Nine studies were identified (489 patients; 959 eyes, range 16 to 394); six RCTs (382 eyes, range 16 to 112) and three comparative studies (577 eyes, range 90 to 394, data from table one; 958 for eyes stated in text) Jadad scores for the RCTs were 3, 4 and 5 for two studies each; and for the comparative studies, 2 for one study and 1 for two studies. Where reported, withdrawals ranged from zero to 12.7%. Follow-up ranged from three to 12 months. There were no significant differences in pre-operative demographic features and other factors that could influence surgery between groups.

There were no significant differences for off-flap versus on-flap epi-LASIK for: postoperative manifest refractive spherical equivalent ($I^2=15\%$; eight comparisons); within ±0.5D of target refraction ($I^2=0\%$; five studies); or loss of at least one line of best spectacle-corrected visual acuity ($I^2=0\%$; five studies). The incidence of severe eye pain within the first 24 hours after operating was significantly lower for off-flap versus on-flap epi-LASIK (OR 0.43, 95% CI 0.19 to 0.99; $I^2=0\%$; four studies). However, the authors suggested that the difference was not significant. There was no significant difference between off-flap and on-flap groups for corneal haze grade at least one after three months ($I^2=0\%$; six comparisons) or after over six months ($I^2=0\%$; seven comparisons).

The mean logMAR uncorrected visual acuity was borderline significantly better for the off-flap group versus the on-flap group after three days (WMD -0.13, 95% CI -0.26 to 0.00; $I^2=78\%$; four studies) and after five days (WMD -0.17, 95% CI -0.30 to -0.04; $I^2=88\%$; five studies) but not at the end of follow-up (≥3 months) (WMD 0.00, 95% CI -0.03 to 0.04; $I^2=0\%$; six studies). There was significantly faster epithelial healing for off-flap versus on-flap epi-LASIK (WMD -1.12, 95% CI -1.59 to -0.64; $I^2=90\%$; seven comparisons).

Subgroup analyses found study design did not affect treatment outcomes. There was no evidence for publication bias.

Authors' conclusions
Off-flap and on-flap epi-LASIK had equal visual and refractive outcomes, and postoperative pain, for the treatment of myopia. Off-flap epi-LASIK had more rapid re-epithelialisation and visual recovery compared with on-flap epi-LASIK.

CRD commentary
The review addressed a well-defined question in terms of study design, participants, interventions and relevant outcomes. The search was adequate but only published studies were included and it was not reported whether studies published in any language were included, so some relevant studies may have been missed. Study quality was assessed using relevant criteria.

The included RCTs were of average to high quality. Efforts were made to reduce error and bias in quality assessment and data extraction but none were reported for study selection. Relevant study details were reported, particularly for patients, but it was not clearly explained why two studies appeared to have two sets of results. No units were reported for epithelial healing time. The methods of synthesis seemed appropriate. It would have been useful to know whether the heterogeneity of the meta-analyses for the RCTs alone was lower than that for all studies. There was a high level of study heterogeneity for the significant results and most of the included studies were small. The authors did not report the significance of some results correctly in the text, such as the result for severe eye pain.

In view of the limited number of studies of predominately small size, study variability and short follow-up duration, the conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors implied that the rate of epithelial healing was important in preventing adverse events.

Research: The authors recommended further high quality comparative clinical trials with larger sample sizes and follow-up periods to confirm these results, and specifically to assess post-operative pain using a uniform pain questionnaire and time of assessment. Further studies were also required to determine whether Mitomycin C was a more significant contributor to postoperative pain, healing, and visual outcomes with epi-LASIK.

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