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RE: Ang et al.: Randomized clinical trial comparing femtosecond LASIK and small-incision lenticule extraction

(*Ophthalmology*. 2020;127:724–730)

TO THE EDITOR: We commend the authors for undertaking a much needed prospective, paired-eye clinical trial in their article.[1]

The study design was a noninferiority trial using "previously published sample size calculation of 67 participants"[1] as a sufficient size to meet the study endpoint. This number assumed the main outcomes measure of refractive predictability, defined as eyes achieving a postoperative spherical equivalent within ±0.50 diopter (D) of the intended target, to be 82% and 92% in the LASIK and SMILE groups, respectively.[2] The 2012 "study protocol for a randomized, noninferiority trial"[2] used the 400-Hz WaveLight Eye-Q excimer laser, with 3M postoperative outcomes.[2] However, the current study[1] used the WaveLight EX500 laser, included 12M outcomes, and the abstract and discussion only report on ±1.00 D predictability.[1]

The study design assumption[2] that refractive predictability would be significantly lower in the LASIK control group (82%) versus the experimental SMILE group (92%), was inaccurate, and resulted in a large underestimation of the sample size required to test a "difference between 2 independent proportions"[1] and reach the defined 80% power, 5% significance level, and a 10% noninferiority limit. Recalculating the sample size with an assumption using the actual 3M study outcomes (LASIK 92%, SMILE 87%) shows the need for 924 eyes,[3] or 474 eyes[3] using the 12M data (91% vs 88%), much more than the study's 134 eyes. The study reports "a proportional difference of 6% (95% [confidence interval], −5% to 17%),"[1] where the upper limit of the 95% confidence interval (17%) exceeds the predefined 10% noninferiority limit. Given the above, and the inadequate sample size, the conclusion of the study should reflect that the primary outcomes measure of ±0.50 D predictability could not statistically validate that SMILE was noninferior to LASIK.

The study states that "postoperative astigmatism was similar between SMILE and LASIK eyes,"[1] but does not discuss the difference at 12M, where 14% of LASIK vs 6% of SMILE eyes had residual astigmatism of >0.50 D (Figs 1G, 2G in the original article). What could explain the clinically meaningful lower astigmatism accuracy in LASIK?

A closer look (Figs 1H, 2H in the original article) reveals identical target-induced astigmatism values in both LASIK and SMILE groups (target-induced astigmatism: 0.72 vs 0.73 D), but a large difference in the surgically induced astigmatism (1.01 vs 0.83 D).[1] By calculating the ratio between the average surgically induced astigmatism and target-induced astigmatism, we derive the correction index[4] to be 1.40 LASIK and 1.14 SMILE, with 1.00 being a perfect correction. This demonstrates a large 40% astigmatism overcorrection in the LASIK group.

The study states that "refractive outcomes of SMILE may improve further with nomogram adjustment,"[1] but does not discuss how the use of an appropriate nomogram would have benefited the LASIK eyes most and could have avoided the large astigmatism overcorrection.

This overcorrection may explain why only 83% and 22% of LASIK eyes achieved 20/20 and 20/15 uncorrected distance visual acuity postoperatively,[1] a lower than expected result considering the use of the latest technology excimer laser (WaveLight EX500). In contrast, a recent EX500 LASIK study with a larger sample size (n = 254) and similar preoperative spherical equivalent (−5.15 ± 2.41 D) reports >90% at 20/20 and 56% at 20/15 uncorrected distance visual acuity postoperatively.[5] Had the authors used a better nomogram, there is a high probability that the main and secondary outcomes measures in the LASIK group would have been superior to the SMILE group, and the study would have failed to demonstrate that SMILE is noninferior to LASIK.

In summary, we agree that SMILE produced promising outcomes. However, we believe the study methodology required a much greater number of eyes to draw more meaningful results, with the upper limit of the 95% confidence interval (17%) exceeding the predefined 10% noninferiority limit. Therefore, the primary outcomes measure of SMILE accuracy being noninferior to LASIK could not be met. As for the secondary outcomes measures, the statement that "SMILE was similar to LASIK at least in terms of predictability, efficacy, stability, and residual astigmatism"[1] could likely not be validated if the trial were to be repeated with a more accurate LASIK nomogram, which would eliminate the large astigmatism overcorrection and bring the LASIK results in line with literature outcomes,[5] and those of our own experience. This is an important study limitation that should be understood.

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