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Article in *Journal of Refractive Surgery* · January 2012

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# IntraLase Femtosecond Laser vs Mechanical Microkeratomes in LASIK for Myopia: A Systematic Review and Meta-analysis

Shihao Chen, MD, OD, MSc; Yifan Feng, MD; Aleksandar Stojanovic, MD; Mirko R. Jankov II, MD, PhD; Qinmei Wang, MD

## ABSTRACT

**PURPOSE:** To evaluate the safety, efficacy, and predictability of IntraLase (Abbott Medical Optics) femtosecond laser-assisted compared to microkeratome-assisted myopic LASIK.

**METHODS:** A comprehensive literature search of Cochrane Library, PubMed, and EMBASE was conducted to identify relevant trials comparing LASIK with IntraLase femtosecond laser to LASIK with microkeratomes for the correction of myopia. Meta-analyses were performed on the primary outcomes (loss of  $\geq 2$  lines of corrected distance visual acuity [CDVA], uncorrected distance visual acuity [UDVA] 20/20 or better, manifest refraction spherical equivalent [MRSE] within  $\pm 0.50$  diopters [D], final refractive SE, and astigmatism), and secondary outcomes (flap thickness predictability, changes in higher order aberrations [HOAs], and complications).

**RESULTS:** Fifteen articles describing a total of 3679 eyes were identified. No significant differences were identified between the two groups in regards to a loss of  $\geq 2$  lines of CDVA ( $P=.44$ ), patients achieving UDVA 20/20 or better ( $P=.24$ ), final UDVA ( $P=.12$ ), final mean refractive SE ( $P=.74$ ), final astigmatism ( $P=.27$ ), or changes in HOAs. The IntraLase group had more patients who were within  $\pm 0.50$  D of target refraction ( $P=.05$ ) compared to the microkeratome group, and flap thickness was more predictable in the IntraLase group ( $P<.0001$ ). The microkeratome group had more epithelial defects ( $P=.04$ ), whereas the IntraLase group had more cases of diffuse lamellar keratitis ( $P=.01$ ).

**CONCLUSIONS:** According to the available data, LASIK with the IntraLase femtosecond laser offers no significant benefits over LASIK with microkeratomes in regards to safety and efficacy, but has potential advantages in predictability. [*J Refract Surg.* 2012;28(1):15-24.] doi:10.3928/1081597X-20111228-02

**L**aser in situ keratomileusis (LASIK) is the most common procedure for corneal refractive surgery to correct myopia.<sup>1</sup> One of the critical steps in this procedure is creation of the corneal flap. Traditionally, the flap is created using mechanical microkeratomes, but femtosecond laser technology has emerged as an alternative.<sup>2</sup>

The femtosecond laser is a focused infrared (1053 nm) laser using ultrafast pulses of 100-femtosecond ( $100 \times 10^{-15}$  second) duration. Each laser pulse generates a small amount of microplasma, which results in microscopic gas bubbles in the interface and creates the flap. During treatment, the cornea is flattened with a suction-applanation lens to immobilize the eye and allow treatment of a geometrically simpler planar cornea.<sup>2,3</sup> Adjacent pulses are scanned across the cornea in a controlled pattern without causing significant inflammation or damage to the surrounding tissue, which possibly results in safer and more predictable flaps.<sup>4,5</sup>

The IntraLase FS laser (Abbott Medical Optics, Santa Ana, California) was introduced in late 2001 and its use is growing rapidly. Numerous studies<sup>6-11</sup> have described the clinical outcomes of patients who underwent LASIK with the IntraLase femtosecond laser versus microkeratomes. However, the results of these studies have not been consistent. Some studies have found few differences in outcome between the techniques,<sup>7,8</sup> whereas others have suggested more favorable outcomes with the IntraLase femtosecond laser.<sup>6,9-11</sup>

The current study is a meta-analysis of existing comparative studies using IntraLase femtosecond laser or mechanical microkeratomes for flap creation in LASIK for myopia. The aim of the analysis was to detect possible differences in terms of safety, efficacy, and predictability of outcomes.

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*Received: February 14, 2011; Accepted: October 13, 2011*

## MATERIALS AND METHODS

The meta-analysis was performed according to generally accepted methods.<sup>12</sup>

### SEARCH STRATEGY

Reports of clinical trials comparing femtosecond laser and microkeratomes in corneal flap creation were identified through a systematic search of PubMed, EMBASE, and the Cochrane Controlled Trials Register through January 1, 2011. A comprehensive search was conducted using the following terms: “femtosecond laser” or “IntraLase” AND “microkeratome” or “keratome.” No language restriction was used. Appendix 1 (available online at [www.slackjournals.com/jrs](http://www.slackjournals.com/jrs)) shows the complete search strategy. Citations initially selected by a systematic search were first retrieved as title and/or abstract and screened independently by two reviewers (S.H.C., Y.F.F.). Potentially relevant reports were retrieved as complete manuscripts and assessed for compliance with inclusion and exclusion criteria. The reference lists of original reports and review articles retrieved by the search were reviewed for additional studies not yet included in the computerized databases.

### INCLUSION AND EXCLUSION CRITERIA

The following selection criteria were used to identify published studies for inclusion in this meta-analysis: 1) controlled clinical studies, including prospective randomized controlled trials and nonrandomized comparative studies; 2) population consisting of patients with any degree of myopia, no significant copathology, no history of ocular surgery, and no systemic disease associated with impaired or abnormal wound healing; 3) all eyes treated by LASIK comparing flap creation with IntraLase femtosecond laser and microkeratomes; and 4) outcome measures based on a standardized format proposed by Reinstein and Waring<sup>13</sup> and the safety and efficacy measures used in United States Food and Drug Administration (FDA) refractive surgery clinical trials.<sup>14</sup> At least one of the primary outcome measures was required.

### OUTCOME MEASURES

The primary outcome measures for inclusion were safety, efficacy, and predictability. The safety measure was a loss of  $\geq 2$  lines of corrected distance visual acuity (CDVA). The efficacy measure was the proportion of patients achieving an uncorrected distance visual acuity (UDVA) of 20/20 or better and final UDVA in logMAR. The predictability measure was a final manifest refraction spherical equivalent (MRSE) and cylinder, MRSE within  $\pm 0.50$  diopters (D) of the target. Other secondary outcomes, such as flap thickness pre-

dictability (difference between actual and intended flap thickness), changes in higher order aberrations (CHOAs), and complications, were also compared. Because of the variable follow-up time and an insufficient number of published articles for separate analysis at each time point, the data reported at the end of follow-up were pooled for comparison.

We computed the induced change in the root-mean-square (RMS) of HOAs based on the preoperative Zernike coefficient compared to the postoperative value. When the mean and standard deviation (SD) of the CHOAs were not available, they were calculated using the following formulas<sup>15</sup>:

$$\text{CHOAs} = \text{HOAs}_{\text{endpoint}} - \text{HOAs}_{\text{baseline}} \quad \text{and}$$

$$\text{SDCHOAs} = (\text{SD}_{\text{baseline}}^2 + \text{SD}_{\text{endpoint}}^2 - \text{SD}_{\text{baseline}} \times \text{SD}_{\text{endpoint}})^{1/2}.$$

### DATA EXTRACTION AND QUALITY ASSESSMENT

Two reviewers (S.H.C., Y.F.F.) independently extracted data and assessed the methodological quality of the trials. Results were compared and any discrepancies between the reviewers' results were resolved by discussion (S.H.C., Y.F.F.) or consensus involving a third reviewer (Q.M.W.) when necessary. A customized form was used to record the authors of each study, country and year of publication, study design, the IntraLase frequency and type of microkeratome, sample size, duration of the trial, and preoperative mean MRSE.

The methodological quality of the randomized controlled trials included in the meta-analysis were assessed according to the Jadad composite scale,<sup>16</sup> allocating 1 point for the presence of each of the following: randomization, masking, and participant withdrawals/dropouts. If randomization and blinding were appropriate, 1 additional point was added for each. Thus, the total score ranged from 0 to 5. Studies scoring  $< 3$  points were considered to be of low quality. Individual components of the Jadad scale were also used to create a 3-point scale based on blinding and participant attrition to assess the methodological quality of cohorts.

### STATISTICAL ANALYSIS

Not all trials reported the outcomes of interest. Separate meta-analyses were performed for each comparison and outcome. A pooled risk ratio (RR) with 95% confidence interval (CI) was calculated for dichotomous outcomes. For the continuous outcomes, the weighted mean difference (WMD) or standardized mean difference (SMD) with 95% CI was calculated. Statistical heterogeneity was tested using the chi-square and  $I^2$  statistic, which indicates the variability in effect estimates associated with heterogeneity rather

than chance. Considering the different clinical characteristics among study groups and the variation of sample sizes, we assumed that heterogeneity was present even when no significance was identified and decided to use a random-effects model.<sup>17</sup> Sensitivity analysis was performed by excluding nonrandomized control trials. Additionally, several subgroup analyses were performed regarding different models of microkeratome and frequencies of IntraLase. A  $P$  value  $<.05$  was considered significant except for tests of heterogeneity, in which a value of  $.01$  was used. Publication bias was assessed with the Begg funnel plot and Egger weighted regression for funnel plot asymmetry.<sup>18</sup> Publication bias was considered significant if the Egger test was significant ( $P<.05$ ) and the Begg plot suggested bias. All statistical analyses were performed using RevMan software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom) and STATA (version 10; StataCorp, College Station, Texas).

## RESULTS

### IDENTIFICATION AND SELECTION OF STUDIES

Study selection is summarized in Figure 1. The literature search identified 223 articles. A total of 30 potential controlled clinical trials relevant to a comparison of the IntraLase femtosecond laser and mechanical microkeratome were identified through the search.<sup>6-11,19-42</sup> Fifteen studies were excluded; 13 lacking primary outcome data,<sup>19-31</sup> 1 study for hyperopia,<sup>32</sup> and 2 reporting on the same subjects<sup>9,33</sup> integrated into one study.<sup>9</sup> Thus, a total of 15 eligible studies were included in the final meta-analysis.<sup>6-11,34-42</sup>

### STUDY CHARACTERISTICS AND QUALITY

The 15 studies (10 randomized controlled trials<sup>6-9,34-36,40-42</sup> and 5 nonrandomized controlled trials<sup>10,11,37-39</sup>) included a total of 3679 eyes (1733 assigned to the IntraLase group and 1946 assigned to the microkeratome group) with myopia from 0 to  $-15.75$  D undergoing LASIK. Sample size varied from 16 to 2000 across studies. Of 15 selected studies published between 2004 and 2010, 5 reported random selection for the use of IntraLase in 1 eye and microkeratome in the other eye for each patient,<sup>7,8,34,40,42</sup> and 5 reported the data with a follow-up of  $\geq 12$  months.<sup>8,33,39-41</sup> When two or more types of microkeratomes were used in 1 article, we combined them into a single group according to the Cochrane Collaboration guidelines.<sup>15</sup> The characteristics and quality of the included trials are summarized in the Table and Appendix 2 (available online at [www.slackjournals.com/jrs](http://www.slackjournals.com/jrs)).

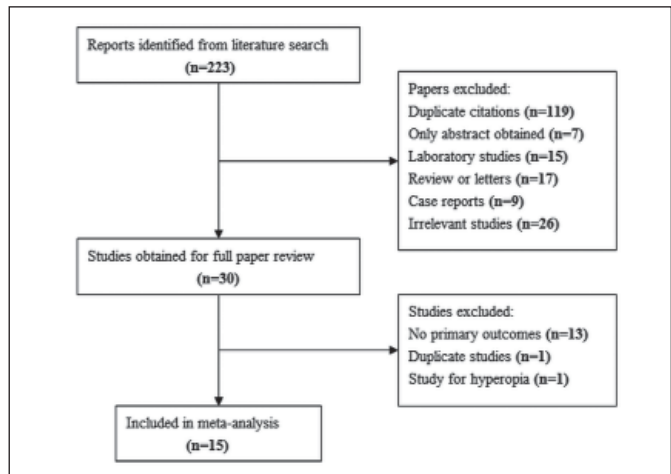


Figure 1. Results of the literature search strategy.

### PRIMARY OUTCOME MEASURES

*Loss of Two or More Lines of Corrected Distance Visual Acuity.* Ten studies reported data for the proportion of patients losing  $\geq 2$  lines after surgery (1472 eyes in the IntraLase group and 1653 eyes in the control group).<sup>6-11,34,36,38,41</sup> Examination of the forest plot demonstrated that no patient lost  $\geq 2$  lines of CDVA in 5 studies.<sup>6,7,9,10,41</sup> The remaining 5 studies<sup>8,11,34,36,38</sup> reported no significant difference between the two groups (RR 1.33; 95% CI: 0.64-2.77;  $P=.44$ ) (Appendix 3, available online at [www.slackjournals.com/jrs](http://www.slackjournals.com/jrs)). A sensitivity analysis was performed to examine the effect of excluding the cohort studies,<sup>10,11,38</sup> but this did not alter the results (RR 2.76; 95% CI: 0.75-10.17;  $P=.13$ ).

*Uncorrected Distance Visual Acuity 20/20 or Better.* Nine publications reported the proportion of patients achieving UDVA of 20/20 or better at the end of follow-up.<sup>6,8,10,11,34,38,39,41,42</sup> Analysis of these data revealed that the difference in the proportion of participants who had UDVA of 20/20 or better after treatment between the two groups was not significant (RR 1.02; 95% CI: 0.99-1.06;  $P=.24$ ) (Fig 2). Sensitivity analysis was performed to examine the effect of excluding the cohort studies,<sup>10,11,38,39</sup> but this did not alter the results (RR 1.04; 95% CI: 0.95-1.14;  $P=.40$ ).

*Final Uncorrected Distance Visual Acuity (logMAR).* Seven studies reported the final postoperative mean UDVA.<sup>7,9,34,36,37,40,41</sup> Follow-up ranged from 3 to 48 months. Analysis of these data showed no difference between the IntraLase and microkeratome groups (WMD  $-0.01$ ; 95% CI:  $-0.04$ - $0.02$ ;  $P=.12$ ) (Fig 3). Sensitivity analysis was performed to examine the effect of excluding the cohort study,<sup>37</sup> but it did not alter the results (WMD  $-0.01$ ; 95% CI:  $-0.03$ - $0.00$ ;  $P=.17$ ).

*Postoperative Refractive Spherical Equivalent and*

TABLE  
**Characteristics of Studies Included in the Meta-analysis Comparing the IntraLase Femtosecond Laser and Microkeratomes for LASIK**

| Study  | Design     | Surgical Procedure                                   | Location       | FS Group |                          | MK Group   |                          | Follow-up (mo) |
|--|------------|--|----------------|----------|--------------------------|------------|--------------------------|----------------|
|  |            |  |                | Eyes (n) | Preop Mean SE (D)        | Eyes (n)   | Preop Mean SE (D)        |                |
| Chan et al (2008) <sup>8</sup>               | Randomized | IntraLase FS 15 kHz<br>Hansatome                     | United States  | 51       | -3.76±1.41               | 51         | -3.77±1.40               | 12             |
| Durrie & Kezirian (2005) <sup>42</sup>       | Randomized | IntraLase FS<br>Hansatome                            | United States  | 51       | -3.59                    | 51         | -3.59                    | 3              |
| Montés-Micó et al (2007) <sup>9</sup>        | Randomized | IntraLase FS<br>Carriazo-Barraquer                   | Spain          | 100      | -2.85±1.79               | 100        | -2.90±1.76               | 6              |
| Patel et al (2007) <sup>7</sup>              | Randomized | IntraLase FS 15 kHz<br>Hansatome                     | United States  | 21       | -4.02±1.61               | 21         | -4.15±1.62               | 6              |
| Tran et al (2005) <sup>6</sup>               | Randomized | IntraLase FS 10 kHz<br>Hansatome                     | United States  | 8        | -2.58                    | 8          | -2.58                    | 3              |
| Javaloy et al (2007) <sup>34</sup>           | Randomized | IntraLase FS 15 kHz<br>Moria M2                      | Spain          | 100      | -3.98±1.89               | 100        | -4.76±2.08               | 3              |
| Alió et al (2008) <sup>36*</sup>             | Randomized | IntraLase FS 30 kHz<br>Moria M2<br>Carriazo-Pendular | Spain          | 22       | -4.11±1.10               | 22         | -3.99±1.22               | 3              |
| Buzzonetti et al (2008) <sup>35</sup>        | Randomized | IntraLase FS<br>Hansatome                            | Italy          | 23       | -6.25±3.6                | 24         | -5.20±3.30               | 12             |
| Muñoz et al (2010) <sup>41</sup>             | Randomized | IntraLase FS 15 kHz<br>Carriazo-Barraquer            | Spain          | 48       | -3.98±2.35               | 50         | -3.80±1.83               | 48             |
| Calvo et al (2010) <sup>40</sup>             | Randomized | IntraLase FS 15 kHz<br>Hansatome                     | United States  | 21       | -4.52±1.62               | 21         | -4.37±1.61               | 36             |
| Lim et al (2006) <sup>10</sup>               | Cohort     | IntraLase FS<br>Hansatome                            | Korea          | 28       | -5.20±2.20               | 27         | -4.70±1.50               | 3              |
| Kezirian & Stonecipher (2004) <sup>11*</sup> | Cohort     | IntraLase FS<br>Hansatome<br>Carriazo-Barraquer      | United States  | 106      | -4.06±1.39               | 143<br>126 | -4.62±1.73<br>-3.82±1.48 | 3              |
| Tanna et al (2009) <sup>38</sup>             | Cohort     | IntraLase FS 60 kHz<br>Evo One Use-Plus              | United Kingdom | 1000     | -2.11±0.69               | 1000       | -2.07±0.69               | 3              |
| Li et al (2010) <sup>39</sup>                | Cohort     | IntraLase FS 15 kHz<br>Moria M2                      | China          | 134      | -8.99±1.85               | 140        | -8.88±1.64               | 12             |
| Rosa et al (2009) <sup>37†</sup>             | Cohort     | IntraLase FS 60 kHz<br>Hansatome<br>Zyoptix XP       | Portugal       | 40       | -4.48±2.55<br>-5.60±1.05 | 20<br>20   | -4.46±0.41<br>-5.62±2.53 | 3              |

FS = femtosecond laser, MK = microkeratome, SE = spherical equivalent

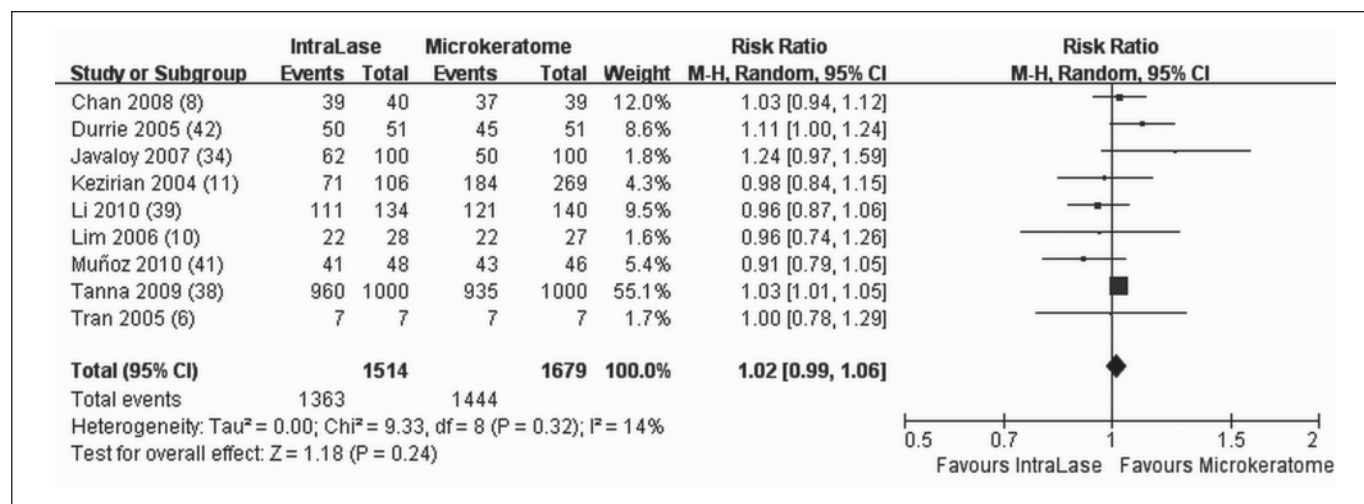
\*Two microkeratomes were included in these studies.

†Four groups were included in this study—group 1: Hansatome; group 2: Zyoptix XP; group 3: IntraLase; group 4: IntraLase after 20 minutes.

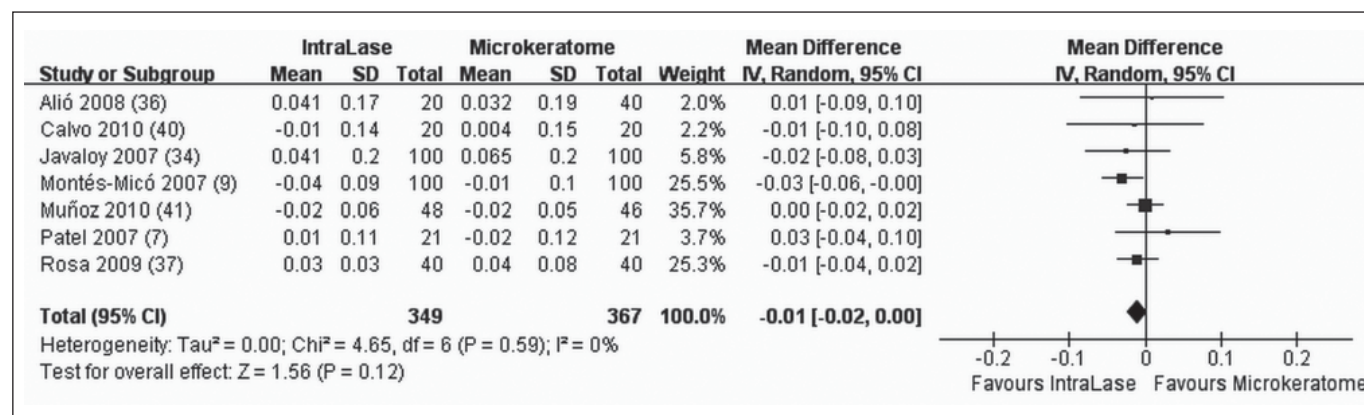
Cylinder. Of the 15 studies, 12 reported data for postoperative mean refractive SE.<sup>7-10,34-37,39-42</sup> No significant difference was identified in the postoperative mean SE between the two groups (WMD -0.01; 95% CI: -0.05-0.04; *P*=.74) (Appendix 4, (available online at [www.slackjournals.com/jrs](http://www.slackjournals.com/jrs)). Sensitivity analysis was performed to examine the effect of the excluded cohort studies,<sup>10,37,39</sup> but this did not alter the results (WMD 0.00; 95% CI: -0.06-0.06; *P*=.95).

Nine studies reported postoperative mean residual cy-

lindrical errors.<sup>6,7,10,11,36,37,39,40,42</sup> One study<sup>42</sup> found that the mean astigmatism results were significantly better in the IntraLase group, and the remaining eight studies reported no significant difference between the two groups. The results showed no significant difference in the postoperative refractive cylinder between the two groups (WMD -0.03; 95% CI: -0.08-0.02; *P*=.27) (Fig 4). Sensitivity analysis was performed to examine the effect of the excluded cohort studies,<sup>10,11,37,39</sup> but this did not alter the results (WMD 0.00; 95% CI: -0.06-0.06; *P*=.95).



**Figure 2.** Proportion of eyes with uncorrected distance visual acuity 20/20 or better after IntraLase femtosecond laser versus microkeratome LASIK. CI=confidence interval, df=degrees of freedom, I<sup>2</sup>=extent of inconsistency, Z=overall effect



**Figure 3.** Mean uncorrected distance visual acuity (logMAR) after IntraLase femtosecond laser versus microkeratome LASIK. SD=standard deviation, CI=confidence interval, df=degrees of freedom, I<sup>2</sup>=extent of inconsistency, Z=overall effect

*Postoperative Refraction Within  $\pm 0.50$  D of Target Refraction.* Data were collected from 11 studies including a total of 3487 eyes (1650 eyes in the IntraLase group and 1837 eyes in the microkeratome group) with refractive error from 0.0 to  $-15.75$  D.<sup>7-11,34,36,38,39,41,42</sup> The forest plot for this outcome showed that more of the studies<sup>9,11,36,38,39,42</sup> had a greater proportion of patients with postoperative refraction within  $\pm 0.50$  D in the IntraLase group than the microkeratome group, whereas one study<sup>34</sup> reported contradictory findings. Significant heterogeneity was detected between study results (I<sup>2</sup>=62%). However, no heterogeneity was found when the study by Kezirian and Stonecipher<sup>11</sup> was excluded (I<sup>2</sup>=0%). Although the likelihood of achieving this outcome was greater in the IntraLase group (RR 1.05; 95% CI: 1.00-1.10) (Fig 5), this finding was not significant (P=.05). Sensitivity analysis was performed to examine the effect of the excluded cohort studies,<sup>10,11,38,39</sup> but this did not alter the results (RR 1.03; 95% CI: 0.99-1.07; P=.12).

## SECONDARY OUTCOME PARAMETERS

*Flap Thickness Predictability.* Six studies reported the values of actual and intended flap thickness.<sup>7,8,11,34,36,37</sup> Flap thickness was measured by confocal microscopy,<sup>7,34</sup> subtraction pachymetry,<sup>8,11,37</sup> and very high-frequency ultrasound scanning.<sup>36</sup> Rosa et al<sup>37</sup> included an IntraLase group in which patients kept their eyes closed for 20 minutes before flap separation and thickness was measured. Analysis of these data revealed that the IntraLase group had a significantly lower deviation from the target thickness than the microkeratome group (SMD  $-0.47$ ; 95% CI:  $-0.70$  to  $-0.24$ ; P<.0001) (Appendix 5, available online at [www.slackjournals.com/jrs](http://www.slackjournals.com/jrs)). Sensitivity analysis was performed to examine the effect of the excluded cohort studies,<sup>11,37</sup> but this did not alter the results (SMD  $-0.82$ ; 95% CI:  $-1.38$  to  $-0.27$ ; P=.006).

*Change in Higher Order Aberrations.* Eight studies reported values for total (whole-eye) and/or corneal

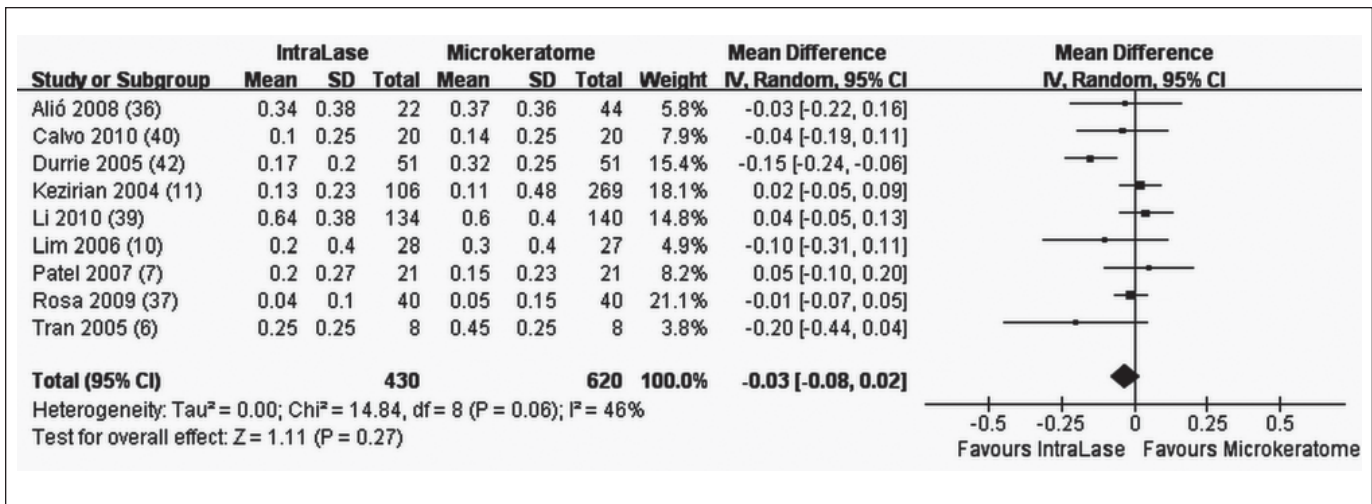


Figure 4. Spherical equivalent refraction after IntraLase femtosecond laser versus microkeratome LASIK. SD=standard deviation, CI=confidence interval, df=degrees of freedom, I<sup>2</sup>=extent of inconsistency, Z=overall effect

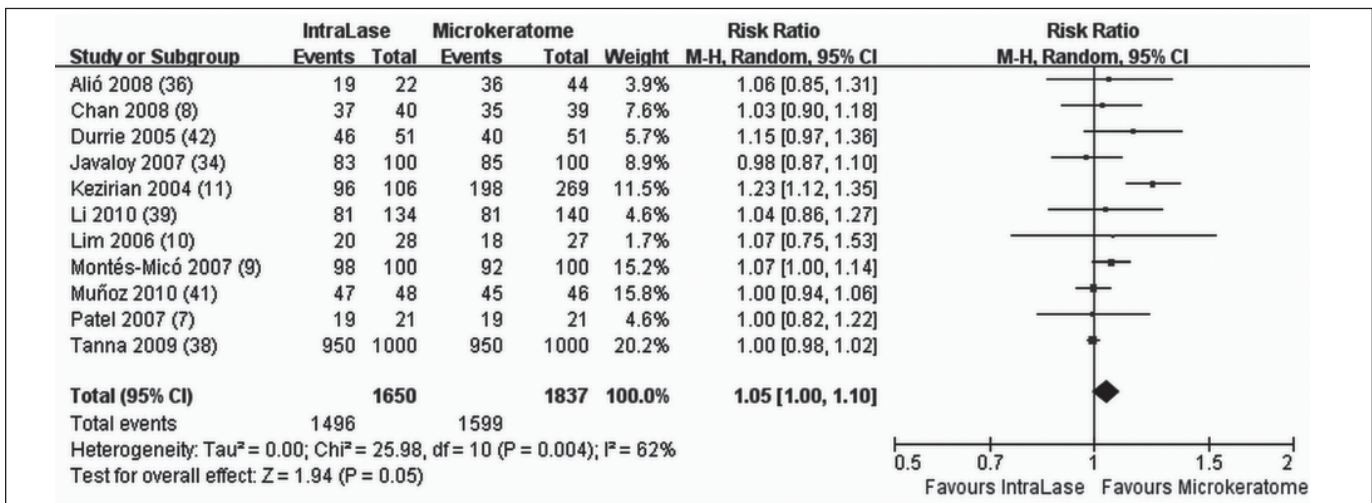


Figure 5. Proportion of eyes within ±0.50 D of target refraction after IntraLase femtosecond laser versus microkeratome LASIK. CI=confidence interval, df=degrees of freedom, I<sup>2</sup>=extent of inconsistency, Z=overall effect

HOAs with different pupil diameters (range: 3.0 to 6.0 mm).<sup>6,8-10,35,39-41</sup> The studies included in this meta-analysis used a variety of systems for analyzing HOAs, such as the Humphrey Atlas (Carl Zeiss Meditec, Jena Germany)<sup>35</sup> and CSO EyeMap (Costruzione Strumenti Oftalmici, Florence, Italy)<sup>40</sup> corneal topography systems, Tomey TMS-2N (Tomey Corp, Nagoya, Japan) topographic data,<sup>9,41</sup> Hartmann-Shack aberrometer (COAS; Wavefront Sciences, Albuquerque, New Mexico),<sup>6</sup> and Zywave<sup>10</sup> (Bausch & Lomb, Rochester, New York) aberrometer. If the systems used in HOA analysis were different across the studies, SMDs were used in this meta-analysis. Because the computation of corneal aberrations from topography is more accurate than computation from whole-eye aberrations, and a direct comparison should be performed only for values computed

for similar pupil diameter, analyses were performed at different pupil diameters (3.0 to 4.0 mm or 5.0 to 6.0 mm) and measures (whole-eye or corneal).

Data were collected from 4 studies including a total of 425 eyes<sup>9,35,40,41</sup> for 3.0- to 4.0-mm diameter optical zones. Significant heterogeneity was detected between study results (I<sup>2</sup>=80%). The results showed no significant difference in the change in whole-eye (SMD 0.25; 95% CI: -0.36-0.85; P=.43) (Appendix 6, available online at [www.slackjournals.com/jrs](http://www.slackjournals.com/jrs)) and corneal HOAs (SMD -0.21; 95% CI: -0.71-0.29; P=.40) between the IntraLase and microkeratome groups. For 5.0- to 6.0-mm-diameter optical zones, data were collected from 8 studies including a total of 851 eyes.<sup>6,8-10,35,39-41</sup> Significant heterogeneity was detected between study results (I<sup>2</sup>≥83%). The results

showed no significant difference in the change in whole-eye (SMD  $-0.32$ ; 95% CI:  $-0.97$ - $0.32$ ;  $P=.33$ ) and corneal HOAs (SMD  $-0.56$ ; 95% CI:  $-1.30$ - $0.18$ ;  $P=.14$ ) between the IntraLase and microkeratome groups. Sensitivity analysis was performed to examine the effect of the excluded cohort studies,<sup>10,39</sup> but this did not alter the results (WMD  $0.11$ ; 95% CI:  $-0.62$ - $0.85$ ;  $P=.76$ ).

### COMPLICATIONS

Three studies reported grade I and II diffuse lamellar keratitis (DLK) 1 day or 1 week after the procedure.<sup>6,8,34</sup> The incidence of DLK was significantly higher in the IntraLase group than the microkeratome group (RR  $6.48$ ; 95% CI:  $1.48$ - $28.38$ ;  $P=.01$ ) (Appendix 7, available online at [www.slackjournals.com/jrs](http://www.slackjournals.com/jrs)). Two studies<sup>8,11</sup> reported loose epithelium in one or two quadrants of patients in the microkeratome group, which was significantly higher than the rate in the IntraLase group (RR  $0.12$ ; 95% CI:  $0.01$ - $0.95$ ;  $P=.04$ ). Additionally, the rate of epithelial ingrowth was not significantly different between the two groups (RR  $0.96$ ; 95% CI:  $0.11$ - $8.72$ ;  $P=.97$ ).

### SUBGROUP ANALYSIS

Subgroup analyses were performed to examine whether differences in key outcomes (loss  $\geq 2$  lines of CDVA, UDVA 20/20 or better, and MRSE within  $\pm 0.50$  D of target) were attributable to different types of microkeratomes and IntraLase frequencies (Appendix 8, available online at [www.slackjournals.com/jrs](http://www.slackjournals.com/jrs)). A greater proportion of patients in the IntraLase group achieved postoperative treatment refraction within  $\pm 0.50$  D of the target refraction than the proportion in the Hansatome group (RR  $1.11$ ; 95% CI:  $1.02$ - $1.21$ ;  $P=.02$ ).

### PUBLICATION BIAS

The Begg test ( $P=.22$  to  $1.0$ ) and Egger test ( $P=.24$  to  $0.97$ ) applied to all primary outcomes did not reveal any publication bias.

### DISCUSSION

Based on available evidence from early comparative studies, we found no differences in the safety, efficacy, or change in HOAs of LASIK with the IntraLase femtosecond laser and LASIK with a mechanical microkeratome. However, a greater proportion of patients in the IntraLase group achieved postoperative refraction within  $\pm 0.50$  D of the target refraction, although no significant differences were found. Flap thickness was more predictable in the IntraLase than in the microkeratome group. Regarding complications, the micro-

keratome group had significantly more intraoperative epithelial defects, and the IntraLase group had significantly more postoperative DLK cases.

One problem with systematic reviews of an evolving technique, as opposed to a drug treatment, is that changes in technology and technique may influence results. The femtosecond laser was first introduced as a 6 kHz laser in 2002, and subsequent evolution of the technology resulted in a gradual increase in frequency, reaching 60 kHz in 2006.<sup>43</sup> Recent reports have documented that although visual results are comparable, the 30-kHz version permits tighter spot/line separation and lower energy per pulse, which creates smoother corneal stromal beds than the previous 15-kHz laser.<sup>44,45</sup> With the release of the 60-kHz platform, even faster rates of flap creation and lower raster bed energies are possible.<sup>46</sup> The frequency of the IntraLase femtosecond laser in most studies included in our analyses was 15 kHz. Therefore, how our findings relate to the outcomes associated with current technology and techniques is unclear. Studies comparing modern microkeratomes to the 60-kHz, or even faster, femtosecond laser would be needed to re-evaluate the relative merits of the technologies.

A major difficulty in combining the results of randomized controlled trials and comparative studies was the variation in follow-up duration. In the current study, only 5 of the 15 studies reported data for  $\geq 1$  year of follow-up, limiting the value of conclusions concerning the long-term stability of refraction. In addition, recovery of corneal innervation and restoration of a normal tear film and ocular surface may take longer than 12 months,<sup>47</sup> which can cause visual fluctuation in the early postoperative period.<sup>48</sup> However, the articles included in this study reported that visual acuity, refraction, and corneal optical quality remained stable in both groups between 3 months and 1 year,<sup>8,39</sup> even up to 4 years<sup>41</sup> of postoperative follow-up. Thus, the data reported at fixed time points of follow-up were pooled, which seems to be feasible from the viewpoint of mere comparison.

No significant difference was identified in the preoperative MRSE between the two groups. However, better predictability was found with the MRSE at the  $\pm 0.50$ -D level in the IntraLase group, although no significant difference was detected ( $P=.05$ ). Moreover, the subgroup analysis showed that more patients in the IntraLase group achieved a postoperative refraction within  $\pm 0.50$  D of the target refraction than in the Hansatome group ( $P=.02$ ). One possible explanation for these findings is that the IntraLase creates uniform and accurate planar flaps rather than meniscus-shaped flaps, which are created by mechanical microkeratomes.<sup>46</sup>



Refractive surgeons have assumed that smoother optical surfaces result in better visual and refractive outcomes following laser refractive surgery.<sup>49,50</sup> Furthermore, Durrie and Kezirian<sup>42</sup> and Kezirian and Stonecipher<sup>11</sup> found a reduction in the overall induced astigmatism in spherical treatments with the IntraLase. The explanation for this finding may lie in the morphology of the flap. IntraLase flaps are circular rather than truncated, extending beneath the hinge, whereas flaps created with mechanical microkeratomes are truncated at the hinge.<sup>11,42</sup> However, other studies were unable to detect significant differences in astigmatic refractive outcomes between the two groups.<sup>7,10,39,40</sup> Only sufficient trials with a larger sample size and adequate follow-up may have the sufficient power to detect differences in predictability.

The results of this meta-analysis showed that both methods are safe and effective. In terms of safety, our data demonstrated that the proportion of patients who lost  $\geq 2$  lines of CDVA in the IntraLase group was similar to the proportion in the microkeratome group. In terms of efficacy, we found no significant difference between the two groups in regards to the proportion of patients achieving UDVA of 20/20 or better and postoperative mean UDVA at the end of follow-up. In consideration of visual quality in patients after refractive surgery, further attention should be paid to the influence of surgery on contrast sensitivity function, rather than visual acuity alone.

Awareness is growing regarding the impact that HOAs have on the quality of vision, especially under low light conditions.<sup>51</sup> Visual symptoms of glare, halos, and starburst have been correlated to HOAs.<sup>52,53</sup> Our meta-analysis indicated that the values of changes in HOAs were not significantly different between the two groups. Nevertheless,  $I^2$  values of  $>80\%$  indicate a high level of between-study heterogeneity. Differences between studies could arise from the different laser systems or microkeratomes used and the degree of myopia corrected. In addition, the cornea undergoes many pathophysiological changes after LASIK, including epithelial thickening,<sup>54</sup> loss of anterior keratocytes,<sup>55</sup> and delayed reinnervation,<sup>56</sup> which can also affect outcomes. More recently, several studies have suggested that the flap-creation modality plays a significant role in LASIK-induced aberrations.<sup>9,22</sup> Femtosecond lasers generate uniform flaps with constant hinge angles, which has been suggested to confer an optical advantage, possibly reducing HOAs.<sup>6</sup> Considering that other factors are also involved in confounding attempts to eliminate all aberrations via refractive surgery, the optimal analysis of changes in corneal aberrations induced by flap creation should be performed before excimer treatment.

Two studies<sup>8,11</sup> reported the complication of epithelial defects, and the result of meta-analysis showed that the microkeratome group had significantly more cases of epithelial defects than the IntraLase group. Sutton and Hodge<sup>57</sup> performed a retrospective analysis of 1000 consecutive IntraLase eyes, and only 0.3% cases had epithelial defects that required a bandage contact lens. In contrast, a large case series (6984 eyes) showed that 9.3% of cases had epithelial defects after LASIK with the Hansatome.<sup>58</sup> More recently, in a retrospective comparison study, Moshirfar et al<sup>27</sup> reported that the microkeratome group had a significantly greater number of epithelial defects (2.6%) than the IntraLase group (0.6%). The IntraLase requires no direct shearing force on the corneal surface during the procedure, whereas the microkeratome pivots the keratome head across the corneal epithelium under high pressure. This difference likely explains the better epithelial preservation seen with the IntraLase.

Diffuse lamellar keratitis is a noninfectious corneal inflammation that sometimes occurs after LASIK.<sup>59</sup> In this meta-analysis, three articles reported DLK observed 1 day or 1 week postoperatively in the IntraLase group, and the incidence of DLK was significantly higher in the 10-kHz and 15-kHz IntraLase groups.<sup>6,8,34</sup> A higher incidence of DLK associated with the femtosecond laser has been hypothesized to be a result of higher energy at the interface<sup>34,60</sup>; thus, higher frequency femtosecond lasers may cause less DLK because they allow lower energy settings. However, some recent studies have not supported this hypothesis.<sup>61,62</sup> Choe et al<sup>61</sup> compared the incidence of DLK with different femtosecond laser frequencies and found no significant differences in the incidence of DLK between the 15-, 30-, and 60-kHz IntraLase lasers. These results are similar to the study by Haft et al,<sup>62</sup> who compared the complications of LASIK flaps created by 15- and 30-kHz IntraLase lasers. Fortunately, all cases of DLK in the three articles included in this meta-analysis were resolved without loss of vision, except one case with grade III DLK, which impacted the refractive outcome. Moshirfar et al<sup>27</sup> showed that, although the IntraLase group had a higher incidence of DLK, the patients did not progress to DLK stage III, and DLK can often be managed with an intense course of topical corticosteroids. Diffuse lamellar keratitis is caused by multiple intrinsic and extrinsic factors, and more studies are needed to help elucidate these mechanisms.

In conclusion, we found that data from early trials comparing LASIK with the IntraLase femtosecond laser and LASIK with microkeratomes for the correction of myopia suggest no significant differences in safety or efficacy. However, the femtosecond laser has a potential advantage in predictability, although this finding was not signifi-

cant. Additional randomized studies are needed to evaluate possible advantages of newer generation femtosecond lasers compared to mechanical microkeratomes.

#### AUTHOR CONTRIBUTIONS

*Study concept and design (S.C., Y.F., Q.W.); data collection (Y.F.); analysis and interpretation of data (S.C., Y.F., A.S., M.R.J.); drafting of the manuscript (S.C., Y.F.); critical revision of the manuscript (A.S., M.R.J., Q.W.); statistical expertise (Y.F.); administrative, technical, or material support (S.C.); supervision (Q.W.)*

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