Corneal biomechanical change assessment using biomechanical waveform analyzer parameters

Contralateral comparison of eyes having femtosecond lenticule extraction and small-incision lenticule extraction for moderate to high myopia

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Published in:
J C R S Online Case Reports

DOI:
10.1016/j.jcro.2018.10.002

Publication date:
2019

Document version:
Accepted manuscript

Document license:
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Citation for published version (APA):
Vestergaard, A. H., Rævdal, P., Ivarsen, A. R., & Hjortdal, J. (2019). Corneal biomechanical change assessment using biomechanical waveform analyzer parameters: Contralateral comparison of eyes having femtosecond lenticule extraction and small-incision lenticule extraction for moderate to high myopia. J C R S Online Case Reports, 7(2), 17-19. https://doi.org/10.1016/j.jcro.2018.10.002

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Download date: 14. Sep. 2023
Detection of corneal biomechanical changes using waveform parameters from The Ocular Response Analyzer: A contralateral comparison of eyes treated with FLEX and SMILE for moderate to high myopia

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Clinical Trials registration reference number: NCT01673503, at www.clinicaltrials.gov

Running head: Case report: FLEX vs. SMILE

Financial Support: Hjortdal J.: Travel reimbursement. Other authors: None.

The authors wish to thank the Region of Southern Denmark for supporting this project
Abstract:

We report the first paired-eye study to directly compare Ocular Response Analyzer (ORA) derived corneal waveform parameters after the two all-femtosecond laser refractive techniques, ReLEx FLEX (FLEX) and ReLEx SMILE (SMILE).

A total of 34 patients, treated with FLEX in one eye, and SMILE in the other for moderate to high myopia, were examined before and 6 months after surgery. Overall, the 37 corneal waveform parameters from the ORA were not able to detect any major differences in corneal biomechanical properties, between the flap-based FLEX procedure and the cap-based SMILE procedure.
Corneal refractive eye surgery affects biomechanical properties by reducing the biomechanical strength due to irreversible corneal lamellar changes. Theoretically, the small incision in the ReLEx SMILE technique, should have biomechanical advantages over flap-based techniques such as ReLEx FLEX and Femtosecond LASIK, due to better preservation of the stronger anterior stroma. This has been demonstrated in a mathematical model by Reinstein et al., a contralateral computational analysis by Seven et al., a finite-element analysis by Roy et al., and in ex vivo porcine eye studies by Spiru et al. However, it still remains a challenge to measure the strength and stability of the cornea in vivo and our knowledge on this area is therefore limited.

Only two commercially available devices state to measure the biomechanical proportions of the cornea in vivo, and both machines use non-contact air puff based tonometry; the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Depew, NY, USA) and the Oculus Corvis ST (CST; Oculus Optik-geräte, Inc., Wetzlar, Germany). The ORA estimates several parameters among which corneal hysteresis (CH) and corneal resistance factor (CRF) are the most prevalent parameters reported when describing corneal viscoelastic properties. The devices are especially used for glaucoma, keratoconus screening, and screening of patients before refractive surgery.

In 2014, we published a paired eye study in which eyes were randomized to receive FLEX in one eye and SMILE in the other eye for treatment of moderate to high myopia. Amongst other parameters, CH and CRF were determined before and 6 months after surgery, in an attempt to detect changes in corneal biomechanical properties related to the different incision sizes. No statistical significant difference was found between the two techniques in that study. However, at the time we were not in possession of the latest ORA software, so
retrieval of the 37 relatively new parameters which describes the waveform of the ORA curve, and the derived keratoconus score, were not available.

Hence, the purpose of this subsequent study was to analyze the 37 new waveform parameters and comparing FLEX and SMILE, in an attempt to further quantify changes in corneal biomechanical properties.

Case report

In the original study, 35 patients (70 eyes) were included in a prospective, single-masked, paired-eye study, registered at www.clinicaltrials.gov (identifier: NCT01673503). Patients were randomized to receive FLEX in one eye and SMILE in the other eye for treatment of moderate to high myopia. All patients had stable myopia and no other ocular diseases. A VisuMax® femtosecond laser (Carl Zeiss Meditec, Jena, Germany) was used to make the refractive cut. Lenticule diameters were the same in both eyes and ranged from 6.00 to 6.50 mm. Flap thickness was 110 to 120 µm, and flap/cap diameter ranged from 7.3 to 8.0 mm. All eyes were left with at least 250 microns of residual stromal bed. For further details, please see the original article and study protocol.6

Concerning corneal waveform parameters: An ocular response analyzer uses bi-directional applanation through brief air-pulses to rapidly deform the cornea in- and outwards, measuring intraocular pressure two times independently. An electro-optical system monitors the central 3 mm curvature of the cornea throughout the deformation and generates an ORA response curve. The 37 new parameters describe different areas, heights, widths, slopes, irregularities etc. of the response curve. For this study, the original raw data were anonymized and sent to the manufacturer of the ORA, and here the newer software (version 3.01) was applied and the new waveform parameters derived, including the so-called keratoconus (KC) score.
Results

In total, 34 of the 35 patients included in the study, completed the 6 months follow-up period. No significant difference (p>0.05) between FLEX and SMILE eyes was found at baseline nor after 6 months for all 37 waveform parameters, including the KC-score. Also, no difference was found when the change in each parameter between the preoperative to 6 months postoperative values from both groups was compared, despite a single parameter (w11 = width of peak1 at the base of the peak1 region). Here, a borderline significant difference between the change in FLEX and SMILE after 6 months (p=0.045), in favour of FLEX was found.

A significant difference was found for the majority of all 37 parameters, including the KC-score, in both the FLEX group and the SMILE group, when preoperative and 6 months data were compared.

Results are presented in Table 1.

Discussion

All previous published contralateral RCT studies comparing SMILE to FLEX or Femtosecond-LASIK,\textsuperscript{6,7,8} have failed to demonstrate any differences between the cap-based SMILE technique and the flap-based techniques when evaluating CH or CRF, although some non-randomized studies (e.g. Wu et al\textsuperscript{9}) have found a difference in favour of the SMILE technique.

In an attempt to enhance our knowledge about corneal biomechanical properties, further evaluation of the ORA waveforms was introduced. In theory, the derived waveforms provide a unique fingerprint for each cornea which may be helpful to differentiate between healthy
and diseased corneas, although very little is known about the clinical significance of these various waveform parameters.\textsuperscript{10}

In this study, the 37 relative new waveform parameters from the ORA, and the resulting KC score, were not able to detect any major differences between the FLEX and the SMILE procedures. The single parameter with a borderline statistical significant value in favour of FLEX could not be related to any clinical relevant change and is speculated to be a result of the multiple significance tests performed. When doing 37 statistical tests, then 1 to 2 parameters will by chance be statistically different with a standard alpha level of 0.05. After correction of multiple comparisons (Bonferroni) the parameter was no longer statistical significant. The majority of the waveform parameters were significantly reduced after either procedure, indicating a weakening of corneal strength, and the changes were highly related to the changes in CCT, as previously demonstrated by other biomechanical parameters (corneal hysteresis and corneal resistance factor).\textsuperscript{6} However, the presumed corneal biomechanical advantage of small incision lenticule extraction (SMILE) compared to the flap-based procedure (FLEX) was not found.

The paired-eye design meant that most sources of variability could be neglected when comparing FLEX and SMILE. However, some potential limitations include variability in patient alignment and corneal centration when performing the air-pulse measurements, and also the ocular pulse amplitude.

To our knowledge, this is the first paired-eye study to directly compare ORA derived waveform parameters after the two all-femtosecond laser refractive techniques, FLEX and SMILE. Future studies should aim for longer follow-up periods to assess the risk of corneal ectasia development over time, but also investigate new in vivo and ex vivo techniques for quantifying corneal biomechanical properties and stability.
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| ORA parameter | SMILE | FLEX | P-values |
|---------------|-------|------|----------|
|               | Pre-op mean score | 6 months mean score | Difference | Pre-op mean score | 6 months mean score | Difference | Pre vs Pre | 6 m vs 6 m | Diff vs Diff |
| aindex        | 9.1   | 8.9  | 0.2      | 9.4       | 8.8*              | 0.7       | 0.063     | 0.389     | 0.247      |
| bindex        | 9.5   | 9.1  | 0.4      | 9.7       | 9.6               | 0.1       | 0.895     | 0.180     | 0.271      |
| p1area        | 5579.2| 2818.0*| 2761.2  | 5425.7    | 2923.9*           | 2501.8    | 0.495     | 0.433     | 0.254      |
| p2area        | 3096.6| 1841.9*| 1254.6  | 3374.4    | 1865.1*           | 1509.3    | 0.244     | 0.870     | 0.199      |
| aspect1       | 27.0  | 25.2 | 1.8      | 28.0      | 25.7              | 2.3       | 0.343     | 0.821     | 0.773      |
| aspect2       | 26.6  | 26.1 | 0.6      | 27.3      | 29.2              | -1.9      | 0.663     | 0.265     | 0.708      |
| uslope1       | 99.5  | 116.0*| -16.5    | 101.7     | 112.2             | -10.5     | 0.354     | 0.496     | 0.572      |
| uslope2       | 111.3 | 130.7 | -19.4    | 123.7     | 139.2             | -15.5     | 0.308     | 0.528     | 0.826      |
| d1area        | 38.8  | 33.7*| 5.1      | 40.1      | 34.5*             | 5.6       | 0.427     | 0.528     | 0.966      |
| w1            | 21.8  | 18.5*| 3.3      | 21.4      | 18.9*             | 2.5       | 0.511     | 0.633     | 0.415      |
| w2            | 17.7  | 14.6*| 3.1      | 18.3      | 13.3*             | 5.0       | 0.557     | 0.157     | 0.115      |
| h1            | 579.2 | 449.6*| 129.6    | 594.5     | 458.3*            | 136.2     | 0.632     | 0.653     | 0.767      |
| h2            | 433.5 | 336.6*| 96.9     | 460.4     | 367.4*            | 93.0      | 0.351     | 0.200     | 0.899      |
| dive1         | 483.0 | 400.6*| 82.4     | 516.3     | 389.9*            | 126.4     | 0.259     | 0.579     | 0.102      |
| dive2         | 345.9 | 233.6*| 112.3    | 372.5     | 268.4*            | 104.0     | 0.335     | 0.150     | 0.774      |
| path1         | 20.7  | 31.5*| -10.9    | 21.9      | 30.8*             | -8.9      | 0.146     | 0.600     | 0.251      |
| path2         | 26.4  | 33.1*| -6.7     | 25.4      | 35.0*             | -9.6      | 0.354     | 0.241     | 0.187      |
| m1area        | 177.3 | 165.7 | 11.6     | 174.3     | 163.6             | 10.7      | 0.744     | 0.699     | 0.953      |
| m2area        | 171.7 | 179.4 | -7.7     | 184.0     | 199.5             | -15.5     | 0.473     | 0.193     | 0.733      |
| s1area        | 97.6  | 118.2*| -20.6    | 102.3     | 113.9             | -11.6     | 0.244     | 0.648     | 0.438      |
| s2area        | 112.3 | 131.6 | -19.3    | 124.8     | 142.2             | -17.5     | 0.295     | 0.407     | 0.918      |
| aplhf         | 1.3   | 1.3   | -0.1     | 1.3       | 1.4               | -0.1      | 0.852     | 0.524     | 0.453      |
| p1area1       | 2517.4| 1109.5*| 1407.9  | 2380.1    | 1137.7*           | 1242.4    | 0.321     | 0.496     | 0.246      |
| p2area1       | 1346.8| 765.9*| 580.9    | 1474.8    | 778.6*            | 696.2     | 0.237     | 0.834     | 0.210      |
| aspect11      | 33.9  | 46.0*| -12.1    | 38.2      | 44.4              | -6.2      | 0.068     | 0.651     | 0.191      |
| aspect21      | 35.6  | 39.8  | -4.3     | 38.2      | 44.3              | -6.1      | 0.477     | 0.315     | 0.763      |
| uslope11      | 88.5  | 110.1*| -21.6    | 98.2      | 106.8             | -8.6      | 0.133     | 0.716     | 0.272      |
| usslope21     | 92.3  | 97.4  | -5.1     | 100.7     | 107.9             | -7.2      | 0.347     | 0.416     | 0.901      |
| dslope11      | 58.1  | 80.2*| -22.1    | 62.8      | 79.0*             | -16.2     | 0.773     | 0.82      | 0.573      |
| dslope21  | 56.1  | 59.5  | -3.5  | 57.6  | 67.3  | -9.7  | 0.394 | 0.154 | 0.550 |
|----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| w11      | 11.8  | 6.9*  | 4.8   | 10.9  | 7.4*  | 3.5   | 0.103 | 0.18  | 0.045 |
| w21      | 8.8   | 6.5*  | 2.3   | 8.7   | 6.1*  | 2.6   | 0.817 | 0.662 | 0.966 |
| h11      | 386.2 | 299.7*| 86.4  | 396.3 | 305.5*| 90.8  | 0.632 | 0.653 | 0.767 |
| h21      | 289.0 | 224.4*| 64.6  | 307.0 | 244.9*| 62.0  | 0.351 | 0.200 | 0.899 |
| path11   | 29.0  | 45.8* | -16.7 | 30.6  | 46.8* | -16.2 | 0.317 | 0.699 | 0.890 |
| path21   | 36.6  | 43.3* | -6.8  | 33.9  | 45.8* | -11.9 | 0.148 | 0.348 | 0.105 |
| KC-score | 1.2   | 0.6*  | 0.6   | 1.3   | 0.6*  | 0.7   | 0.284 | 0.491 | 0.657 |

Table 1. Waveform parameters including keratoconus score (KC-score) from the Ocular Response Analyzer for 34 patients treated with ReLEX FLEX in one eye and ReLEx SMILE in the other.

* indicates p<0.05 when pre-operative values and 6 months post-operative values are compared.