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To cite this article: Elizabeth Wen Ling Lim & Li Lim (2019) Review of Laser Vision Correction (LASIK, PRK and SMILE) with Simultaneous Accelerated Corneal Crosslinking – Long-term Results, Current Eye Research, 44:11, 1171-1180, DOI: 10.1080/02713683.2019.1656749

To link to this article: https://doi.org/10.1080/02713683.2019.1656749
Review of Laser Vision Correction (LASIK, PRK and SMILE) with Simultaneous Accelerated Corneal Crosslinking – Long-term Results

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ABSTRACT

**Purpose:** Laser in-situ keratomileusis (LASIK), photorefractive keratectomy (PRK) and small-incision lenticule extraction (SMILE) are safe and effective refractive surgical procedures. However, complications include regression of treatment and iatrogenic keratectasia which can be severe and sight-threatening. In order to reduce these complications, simultaneous corneal cross-linking (CXL) is currently being added to these refractive procedures. This review analyses current long-term literature (≥1 year follow-up) on refractive surgery and simultaneous CXL (LASIK Xtra, PRK Xtra and SMILE Xtra) to determine its overall safety and efficacy.

**Methods:** A comprehensive literature search of various electronic databases (PubMed, PubMed Central and MEDLINE) was performed up to 9\textsuperscript{February} 2019. Efficacy and safety indices are calculated where possible.

**Results:** Ten relevant studies were found for LASIK Xtra, 4 for PRK Xtra and 1 for SMILE Xtra. The total number of eyes included in this review was 1,189: 347 eyes for LASIK Xtra, 300 eyes for LASIK-only, 298 for PRK Xtra, 204 for PRK-only, 40 for SMILE Xtra and none for SMILE-only. Current studies show that refractive surgery and simultaneous CXL produces comparable or better results in terms of refractive and keratometric stability than refractive surgery alone. However, case reports of complications such as corneal ectasia, diffuse lamellar keratitis and central toxic keratopathy have also recently been published.

**Conclusions:** Simultaneous accelerated CXL and refractive surgery is effective for the treatment of myopia. However, it is as yet unclear if the additional CXL step reduces the incidence of iatrogenic keratectasia. Further long-term comparative studies would be useful in evaluating safety and efficacy of this procedure. More research should also be performed to titrate the UV-A irradiation settings for an optimal outcome.

Introduction

Corneal refractive surgery has evolved tremendously in the past few decades. The first laser photorefractive keratectomy (PRK) was performed almost three decades ago.\textsuperscript{1,2} PRK, though effective, has significant drawbacks such as iatrogenic corneal haze and limited predictability especially for higher diopteric corrections.\textsuperscript{1,2,3} Laser in-situ keratomileusis (LASIK) has since overtaken PRK to become the most commonly performed refractive surgical technique since it has quick visual recovery, good refractive outcomes, a low incidence of corneal haze and minimal post-operative discomfort.\textsuperscript{4} However, LASIK involves the creation of a corneal flap which may weaken the corneal structure and decrease corneal rigidity.\textsuperscript{5,6} This could increase the risk of LASIK regression and post-LASIK ectatic conditions. Small-incision lenticule extraction (SMILE) is a new femtosecond laser technique which does not require corneal flap creation.\textsuperscript{7} It is equally as effective as LASIK and may result in a higher corneal biomechanical strength.\textsuperscript{7}

Iatrogenic keratectasia is a rare but serious complication of refractive surgery. Seiler \textit{et al} reported the first cases of iatrogenic keratectasia in 1998.\textsuperscript{8,9} Reports show a prevalence ranging from 0.02% to 0.6% with a higher incidence of post-LASIK as compared to post-PRK ectasia.\textsuperscript{6,10–12} Recently, reports on post-SMILE ectasia have also emerged.\textsuperscript{13–16} Risk factors for post-LASIK ectasia include pre-operative high myopia or hyperopia, thin corneas and patients with abnormal topography (such as forme fruste keratoconus).\textsuperscript{8,9,17}

In order to prevent the development of iatrogenic keratectasia, simultaneous corneal cross-linking (CXL) and refractive surgery is currently performed in many countries worldwide. CXL was first performed in combination with LASIK (LASIK Xtra, a term introduced by Avedro, Inc., Waltham, MA, USA) before subsequently being used in PRK (PRK Xtra) and SMILE (SMILE Xtra).\textsuperscript{18–20} The initial purpose of CXL was to treat keratoconus and iatrogenic ectasia though currently its uses are expanded to include ectasia prophylaxis and infectious keratitis treatment.\textsuperscript{21–23} CXL uses the combined action of riboflavin and ultraviolet-A (UV-A) to cause photopolymerisation of corneal collagen fibers, enhancing corneal biomechanical strength through the formation of new covalent bonds.\textsuperscript{24,25} Apart from the potential to prevent iatrogenic...
keratectasia, simultaneous CXL could also reduce treatment regression after refractive surgery.\textsuperscript{18,26–28}

However, CXL can have significant complications such as corneal haze and scarring, infective keratitis, sterile infiltrates, delayed epithelial healing and excessive corneal flattening with hyperopic shift.\textsuperscript{22,29–31} It is therefore essential to weigh the long-term benefits and risks of simultaneous CXL and refractive surgery. Long-term studies on this subject are important since iatrogenic keratectasia can occur anywhere from 1 week to several years after refractive surgery.\textsuperscript{32,33} In this systematic review, long term reports (≥1 year) on simultaneous CXL and refractive surgery (LASIK Xtra, PRK Xtra and SMILE Xtra) are analysed to determine the efficacy and safety of this procedure. Efficacy and safety indices are calculated for studies which report visual acuity data.

**Methods**

**Literature search**

A comprehensive literature search of various electronic databases (PubMed, PubMed Central and MEDLINE) was performed up to 9th February 2019. The keywords used were: "laser in situ keratomileusis", "LASIK", "LASIK Xtra", "photo-refractive keratectomy", "PRK", "PRK Xtra", "surface ablation", "laser epithelial keratomileusis", "LASEK", "small incision lenticule extraction", "SMILE", "SMILE Xtra", "crosslinking", "cross-linking", "cross linking" and "CXL". The references of retrieved articles were also searched for other relevant articles. The following types of studies were excluded from our review: (1)studies performed with sequential refractive surgery and CXL, (2)studies with known keratoconus or corneal ectasia patients, (3)in-vitro or animal studies, (4)studies with a follow-up period <1 year, (5)non-English publications. Ten relevant studies were found for LASIK Xtra, 4 for PRK Xtra and 1 for SMILE Xtra. The total number of eyes included in this review was 1,189: 347 eyes for LASIK Xtra, 300 eyes for LASIK-only, 298 for PRK Xtra, 204 for PRK-only, 40 for SMILE Xtra and none for SMILE-only. The average follow-up ranged from 1–4 years. For studies which reported the corrected distance visual acuity (CDVA) and uncorrected distance visual acuity (UDVA) values, efficacy index and safety index were calculated. The following formula was used to calculate efficacy index: mean post-operative UDVA (decimal)/pre-operative CDVA (decimal). The safety index formula used was: mean post-operative CDVA (decimal)/mean preoperative CDVA (decimal).

**Results**

**LASIK Xtra in the treatment of myopia**

There are currently 7 long-term studies (≥1 year follow-up) in the literature on LASIK Xtra in the treatment of myopia, 5 of which are comparative studies, 2 of which are case series. (Table 1)

**Refractive and keratometric results: efficacy and stability**

All comparative studies reported either similar or better long-term refractive and keratometric results (in terms of post-operative spherical equivalent [SE] refraction, efficacy index, UDVA and keratometric values) seen in LASIK Xtra as compared to LASIK alone.\textsuperscript{38–41} Two case series also support these results.\textsuperscript{42,43} The calculated efficacy index for LASIK Xtra in myopia ranges from 0.99–1.16.\textsuperscript{41–43} Kanellopoulos et al reported 1 year results showing that 90.4% of LASIK Xtra eyes had UDVA of 20/20 or better as compared to 85.4% of LASIK-only eyes (p = .042).\textsuperscript{38} In a 2 year comparative study on high myopes, Kanellopoulos et al showed that both the LASIK Xtra group and the LASIK-only group had a similar SE refraction, with 84.6% achieving between 0.50D to 0.00D for the LASIK Xtra group and 81.3% for the LASIK-only group (not significant, p = .0754).\textsuperscript{18} Both 1 and 2 year comparative studies by Kanellopoulos et al showed more keratometric stability in the LASIK Xtra group with no forward keratometric shift as compared to the LASIK-only group (p = .039, one-year study; p = .032, two-year study).\textsuperscript{18,39} Seiler et al conducted a study on myopic patients with high ectasia risk scores of 3–6 and noted similar refractive results in both groups at 1 year follow-up.\textsuperscript{40} Celik et al reported that all LASIK Xtra eyes preserved their post-operative UDVA whereas myopic changes were seen in 2 LASIK-only eyes at 1 year follow-up.\textsuperscript{38} One comparative study (Tomita et al) showed no significant difference in keratometric values in the two groups (p > .05).\textsuperscript{41} Two case series show an improvement in the mean keratometry from 44.5 D preoperatively to 38 D post-operatively in a study by

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**Procedure**

The LASIK Xtra protocol recommended by Avedro is as follows\textsuperscript{34,35}: (1)the LASIK flap is created and laser ablation is done as per usual; (2)with the flap left open, 0.22% riboflavin (Vibex Xtra riboflavin, Avedro) is applied onto the underlying stromal bed and allowed to soak for 45-120s; (3)the stromal bed is irrigated to remove the riboflavin solution and the corneal flap is repositioned; (4)UV-A irradiation through the closed corneal flap is performed at 30 mW/cm\textsuperscript{2} for 45-90s, 1.4–5.4 J/cm\textsuperscript{2} delivered in total (Avedro KXL system, Avedro). There are variations in the protocol in terms of riboflavin concentration, soak time and amount of UV-A energy delivered.

For PRK Xtra, the following procedure is performed\textsuperscript{19}: (1) transepithelial PRK photoablation is performed without the creation of a corneal flap; (2)0.1% riboflavin with hydroxypropyl methylcellulose (Vibex Rapid, Avedro) is applied for 90s and subsequently rinsed off with a chilled balanced salt solution; (3) UV-A irradiation of 30 mW/cm\textsuperscript{2} is performed for 90s (total energy 2.7 J/cm\textsuperscript{2}); (4)0.02% mitomycin C (MMC) is applied for 20s and subsequently rinsed off, followed by bandage lens application. The riboflavin concentration, soak time, UV-A irradiation power and duration vary in different protocols. One study omitted the application of MMC (step 4).\textsuperscript{6}

For SMILE Xtra, the procedure is as follows\textsuperscript{20}: (1)SMILE is performed following the standard protocol\textsuperscript{37}; (2)0.25% riboflavin in saline is injected into the interface and left to diffuse for 60s, after which it is rinsed off with saline; (3)UV-A irradiation of 45 mW/cm\textsuperscript{2} for 75 s (total energy 3.4 J/cm\textsuperscript{2}) is performed. The riboflavin concentration, soak time, UV-A irradiation power and duration may vary between studies.
Table 1. Long term studies (≥1 year) on LASIK Xtra in the treatment of myopia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of eyes (LASIK Xtra, LASIK)</th>
<th>Follow-up (months)</th>
<th>UV power, duration/UV device/UV total energy/riboflavin conc, duration</th>
<th>Pre-op MRSE (D)</th>
<th>Post-op MRSE (D)</th>
<th>Efficacy index</th>
<th>Safety index</th>
<th>Overall outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanellopoulos et al, 2015</td>
<td>Randomised prospective comparative</td>
<td>65, 75</td>
<td>24</td>
<td>30 mW/cm², 80s/Avedro KXL/2.4 J/cm²/0.1% riboflavin, 60s</td>
<td>-6.67 ± 2.14</td>
<td>-0.18 ± 0.17</td>
<td>- -</td>
<td>-</td>
<td>Less refractive shift (P = .065), better keratometric stability (P = .032) in LASIK Xtra group</td>
</tr>
<tr>
<td>Celik et al, 2012</td>
<td>Prospective comparative</td>
<td>4, 3</td>
<td>12</td>
<td>30 mW/cm², 3 min/Avedro KXL/5.4 J/cm²/0.1% riboflavin, 90s</td>
<td>-5.00 to -8.50</td>
<td>Mean sphere</td>
<td>- -</td>
<td>-</td>
<td>All LASIK Xtra eyes preserved UDVA. 2 LASIK eyes had myopic change: ≥ 2 lines UDVA loss</td>
</tr>
<tr>
<td>Kanellopoulos et al, 2014</td>
<td>Prospective comparative</td>
<td>73, 82</td>
<td>12</td>
<td>30 mW/cm², 80s/Avedro KXL/2.4 J/cm²/0.1% riboflavin with dextran, 60s</td>
<td>-6.58 ± 1.98</td>
<td>-0.19 ± 0.17</td>
<td>- -</td>
<td>-</td>
<td>Less refractive shift (P = .063) and better keratometric stability (P = .039) in LASIK Xtra group</td>
</tr>
<tr>
<td>Seiler et al, 2015</td>
<td>Prospective comparative (high ectasia risk score of 3–6)</td>
<td>76, 76</td>
<td>12</td>
<td>9 mW/cm², 5 min/UVX 2000, IROC/2.7 J/cm²/0.5% riboflavin w/o dextran, 2 min</td>
<td>Mean sphere, mean cylinder</td>
<td>-0.21 ± 0.45</td>
<td>- -</td>
<td>-</td>
<td>Similar visual and refractive results in both groups but higher prevalence of transient side effects like DLK and delayed visual rehabilitation in LASIK Xtra group</td>
</tr>
<tr>
<td>Tomita et al, 2014</td>
<td>Comparative</td>
<td>24, 24 FE</td>
<td>12</td>
<td>30 mW/cm², 60s/Avedro KXL/1.8 J/cm²/0.1% riboflavin with 20% dextran, 60s</td>
<td>-4.45 ± 2.18</td>
<td>+0.13 ± 0.38</td>
<td>0.99</td>
<td>1.01</td>
<td>No significant difference in refractive or keratometry (P &gt; .05) results between the 2 groups</td>
</tr>
<tr>
<td>Kanellopoulos et al, 2012</td>
<td>Comparative</td>
<td>43, 42</td>
<td>12 (12–54)</td>
<td>10 mW/cm², 3 min/Pravision/1.8 J/cm²/0.1% riboflavin, 60s</td>
<td>-7.5 ± 2.5</td>
<td>-0.2 ± 0.5</td>
<td>1.09,-</td>
<td>1.09,-</td>
<td>LASIK Xtra appears safe and effective. No ectasia or significant regression observed. LASIK Xtra is effective and safe for improving visual acuity for myopic patients with thin corneas</td>
</tr>
<tr>
<td>Xu et al, 2017</td>
<td>Prospective case series (unsatisfactory corneas)</td>
<td>22, 0</td>
<td>12</td>
<td>30 mW/cm², 90s/Avedro KXL/2.7 J/cm²/0.25% riboflavin, 90s</td>
<td>-5.53 ± 2.27</td>
<td>+0.03 ± 0.82</td>
<td>1.16,-</td>
<td>1.20,-</td>
<td></td>
</tr>
</tbody>
</table>

UV: ultraviolet; conc: concentration; pre-op: pre-operative; post-op: post-operative; MRSE: manifest refraction spherical equivalent; D: diopters; UDVA: uncorrected distance visual acuity; DLK: diffuse lamellar keratitis; FE: fellow eye
Avedro KXL (Avedro, Inc., Waltham, MA, USA); UVX 2000 IROC (IROC Innocross AG, Zurich, Switzerland); Pravision (Pravision, Inc., Menlo Park, CA, USA)

*aEfficacy index was calculated with the formula: mean post-operative UDVA (decimal)/pre-operative CDVA (decimal)*

*bSafety index was calculated with the formula: mean post-operative CDVA (decimal)/mean pre-operative CDVA (decimal)
Safety
LASIK Xtra is a safe procedure for the treatment of myopia. In all studies, none of the LASIK Xtra eyes had any post-operative decrease in CDVA. The calculated safety index for LASIK Xtra in myopia ranges from 1.01–1.20. In the studies which performed endothelial cell count measurements, post-operative endothelial cell density was not different between LASIK Xtra and LASIK-only groups.

In a 2 year study by Kanellopoulos et al, pre-operative and post-operative CDVA were compared. In the LASIK Xtra group, 23 eyes (35.4%) were unchanged, 37 eyes (56.9%) gained 1 Snellen line and 5 eyes (7.9%) gained 2 or more Snellen lines. No eye lost a line. In the LASIK-only group, 26 eyes (34.7%) were unchanged, 45 eyes (60.0%) gained 1 Snellen line, and 3 eyes (4.0%) gained 2 or more lines. However, 1 eye (1.3%) lost 1 line. In comparative studies by Celik et al and Seiler et al and a case series by Kanellopoulos et al, none of the eyes lost any lines. The calculated LASIK Xtra safety index in the case series by Kanellopoulos et al was 1.09.

Tomita et al reported a change in CDVA from −0.20 ± 0.06 (logMAR) pre-operatively to −0.20 ± 0.05 (logMAR) post-operatively in LASIK Xtra group and from −0.19 ± 0.06 (logMAR) pre-operatively to −0.21 ± 0.05 (logMAR) post-operatively in LASIK-only group. Reported safety index was 1.01 (LASIK Xtra) and 1.05 (LASIK-only). Xu et al performed a case series which showed that CDVA improved from 0.89 ± 0.16 (decimal) pre-operatively to 1.07 ± 0.34 (decimal) after 2 years in LASIK Xtra eyes. Calculated safety index was 1.20. Certain transient complications were reported in higher frequency in LASIK Xtra patients as compared to LASIK-only patients. Seiler et al reported a higher prevalence of transient side effects such as DLK and delayed visual rehabilitation in the LASIK Xtra group. No corneal ectasia was seen in either group. Celik et al reported the presence of faint stromal haze (grade 0.5) in LASIK Xtra eyes in the first post-operative week. Two studies by Kanellopoulos et al showed no complications such as epithelial ingrowth, DLK, post-operative haze, or other complications in either group.

LASIK Xtra in the treatment of hyperopia
There are currently 3 long-term studies with ≥1 year follow-up in the literature on LASIK Xtra in the treatment of hyperopia, 2 of which are comparative studies, 1 of which is a case report. (Table 2)

Refractive and keratometric results: efficacy and stability
Both comparative studies reported either similar or better long-term refractive results (in terms of mean SE cycloplegic refraction and efficacy indices) seen in LASIK Xtra as compared with LASIK alone. Kanellopoulos et al reported statistically significant greater regression in LASIK-only eyes (mean 2-year post-operative SE cycloplegic refraction: +0.20) compared to LASIK Xtra eyes (mean 2-year post-operative SE cycloplegic refraction: −0.20) in a two-year comparative study on patients.
with hyperopia or hyperopic astigmatism \( (p = .0001) \). Kanellopoulos et al also reported a statistically significant greater mean keratometric change in LASIK-only eyes as compared to LASIK Xtra eyes \( (p = .001) \) (graph reported, no exact values). In a comparative study with a follow-up of 3–4.5 years \( (5 \text{ LASIK Xtra eyes and 5 matched LASIK-only controls}) \), Aslanides et al found that there were no significant hyperopic regression in the LASIK Xtra group but a suggestive trend towards hyperopic regression in the LASIK-only group \( \text{(specific values not reported)} \). The calculated efficacy indices in the LASIK Xtra group and LASIK-only group were 1.07 and 0.83 respectively.

**Safety**

In a comparative study by Aslanides et al \( (5 \text{ LASIK Xtra eyes and 5 LASIK-only eyes}) \), LASIK Xtra in hyperopia has been shown to be safe. Pre-operative best corrected visual acuity \( \text{(BCVA)} \) was 0.12 \( \text{(logMAR)} \) for LASIK Xtra group, 0.09 \( \text{(logMAR)} \) in LASIK-only group. Post-operative BCVA was 0.017 \( \text{(logMAR)} \) in the LASIK Xtra group and 0.06 \( \text{(logMAR)} \) in the LASIK-only group. Calculated safety indices were 1.27 in the LASIK Xtra group and 1.07 in the LASIK-only group. None of the eyes lost Snellen lines in BCVA. Two eyes gained a Snellen line in the LASIK Xtra group. A comparative 2-year study by Kanellopoulos et al \( (34 \text{ LASIK Xtra eyes and 34 LASIK-only eyes}) \) concluded that both LASIK Xtra and LASIK-only appear safe and effective for the treatment of hyperopia and hyperopic astigmatism \( \text{(actual values not mentioned)} \). Neither of these papers measured endothelial cell counts. Complications of LASIK Xtra in the treatment of hyperopia have been reported. Aslanides et al reported a faint midstromal haze in the LASIK Xtra group on the first post-operative day but this resolved within 1 week. Taneri et al reported the first case of ectasia occurring at 2 years follow-up in a patient who underwent LASIK Xtra for hyperopia. UDVA dropped from 1.0 (decimal) three months post-operatively to 0.25 (decimal) after 2 years in the left eye. Subjective refraction in the left eye was \( +1.50 - 2.00 \times 58^\circ \). CDVA was 0.8 (decimal). Orbscan examination in the left eye showed typical signs of corneal ectasia, including increased anterior and posterior elevation, an inferior steepening in the keratomatrical axial power map, and a reduced minimum corneal thickness.

**PRK Xtra**

Studies on PRK Xtra have only been done on myopic eyes. There are currently 2 comparative studies and 1 case series with \( \geq 1 \) year follow-up in the literature on this subject.  

**Refractive and keratometric results: efficacy and stability**

PRK Xtra has similar or better results as compared to PRK alone in terms of refractive outcomes \( \text{(spherical error, MRSE, UDVA and efficacy index)} \) and stability. Lee et al performed a 1 year comparative study which showed that the PRK Xtra group had a significantly lower spherical error and MRSE than the PRK-only group \( (p < .001 \text{ for both}) \). Though UDVA was significantly better in the PRK Xtra group at 2 weeks and 1 month post-operatively \( (p = .015) \), there was...
no significant difference at 1 year post-operatively ($p = .289$). In this study, similar keratometric changes in both PRK Xtra and PRK-only groups over 1 year follow-up were also reported. Neither group had any progressive flattening or refractive shift. In a 1-year comparative study by Sachdev et al, post-operative uncorrected visual acuity (UCVA) was not significantly different in both groups even though PRK Xtra was performed on statistically significantly thinner corneas ($p < .01$) with corneal tomographic abnormalities ($p = .02$). 954% of the eyes in the PRK Xtra group and 97.4% in the PRK-only group achieved a refractive predictability within 0.50D ($p = .8$). There was no statistical difference in the 1 year mean post-operative MRSE in the two groups. Ohana et al performed a retrospective case series of 98 eyes which underwent the PRK Xtra procedure.[16] Refractive outcome was stable throughout the 1 year follow-up though there was a slight hyperopic drift which was not statistically significant ($p = .10$). Calculated efficacy index was 0.81.

**Safety**

Two studies show that PRK Xtra is safe in the treatment of myopia. In a comparative study by Sachdev et al, 90 eyes (82.56%) in the PRK Xtra group had unchanged CDVA, 1 eye (0.91%) lost one line, 17 eyes (15.59%) gained one line, and 1 eye (0.91%) gained 2 lines. In the PRK-only group, 103 eyes (87.29%) had no change while 15 eyes (12.7%) gained one line in CDVA. Ohana et al reported in a retrospective case series with 98 eyes that CDVA in PRK Xtra eyes changed from 0.06 ± 0.07 (logMAR) pre-operatively to 0.08 ± 0.14 (logMAR) one year post-operatively (calculated safety index: 0.95). Post-operative endothelial cell counts were not different between the two groups PRK Xtra and PRK-only ($p$-values: 0.262 [Lee et al], 0.69 [Sachdev et al]). Complications have been noted in PRK Xtra. Lee et al reported that 1 patient in the PRK Xtra group developed a sterile marginal infiltrate in the early post-operative period which did not affect visual acuity and resolved after topical steroid treatment. No significant complications such as delayed epithelial healing, corneal ectasia or significant corneal haze were observed in either group. Sachdev et al reported no significant complications in either group but some eyes in PRK Xtra group had grade 1 superficial corneal haze which resolved within 6 months. MMC was used in the PRK only group but not in the PRK Xtra group. Ohana et al reported that 51% of treated eyes had corneal haze grade 1 or 2, 3% had grade 3 and 1% had grade 4 corneal haze. There is no mention about the use of MMC in this study. Davey et al reported a case of central toxic keratopathy with an onset of 3 days post-PRK Xtra (3 months post-operatively; UCVA 0.1, BCVA 0.5, refractive $+13.00/-6.50 \times 106^\circ$). No MMC was used during the PRK Xtra procedure in this case.

**SMILE Xtra**

There is only 1 case series on SMILE Xtra with long-term follow-up (≥1 year) in the literature. (Table 4) Ganesh et al performed a case series on 40 eyes of 20 myopic patients with moderate to high risk of ectasia (Randleman Scoring:3) who underwent SMILE Xtra. Mean SE changed from $-5.02 \pm 2.06$D pre-operatively to $-0.24 \pm 0.18$D post-operatively, mean CCT and keratometry decreased from 501 ± 25.90 µm to 415 ± 42.26 µm and 45.40 ± 1.40D to 41.2 ± 2.75D respectively. CDVA remained stable and no complications such as keratitis, ectasia or regression were observed (calculated efficacy index: 1.04). However, 2 eyes developed Grade 2 corneal haze that resolved within 3 months following treatment with topical steroids. One-year post-operative endothelial cell counts did not change from pre-operative values ($p = .22$). CDVA changed from 0.038 ± 0.06 (logMAR) pre-operatively to $-0.073 \pm 0.081$ (logMAR) post-operatively (calculated safety index: 1.29), indicating that SMILE Xtra is a safe procedure.

**Discussion**

**Efficacy**

Overall, combined refractive surgery and simultaneous accelerated CXL (LASIK Xtra, PRK Xtra and SMILE Xtra) is effective in producing good long-term refractive and keratometric results. Comparative studies show that combined refractive surgery and simultaneous accelerated CXL have similar or better efficacies as compared to refractive surgery alone. In LASIK Xtra for myopia, a 1 year comparative study reported better UDVA in the LASIK Xtra group while a 2 year comparative study showed that both the LASIK Xtra and LASIK-only group had comparable SE refraction. Hyperopic LASIK Xtra was shown to be more efficacious than LASIK-only (efficacy index: 1.07 [LASIK Xtra]; 0.83 [LASIK-only]). PRK Xtra had similar or better results as compared to PRK alone in terms of refractive outcomes.
Safety

LASIK Xtra has been shown to be a safe procedure for both myopia and hyperopia. In the studies on myopic LASIK Xtra, no eye had a decrease in CDVA. For myopic LASIK Xtra, calculated safety index ranges from 1.01–1.20. For hyperopic LASIK Xtra, comparative studies by Aslanides et al and Kanellopoulos et al conclude that LASIK Xtra is a safe procedure. However, in the study by Aslanides et al, though the calculated safety index for LASIK Xtra is higher than LASIK-only (1.27 [LASIK Xtra] vs 1.07 [LASIK-only]), the sample size was relatively small with only 5 LASIK Xtra eyes and 5 LASIK-only eyes included. Larger-scale studies are required to make more conclusive comparisons between the safety of the two techniques. A comparative 2-year study by Kanellopoulos et al had a larger sample size (34 LASIK Xtra eyes and 34 LASIK-only eyes) and although they concluded that both LASIK Xtra and LASIK-only appear safe and effective for the treatment of hyperopia and hyperopic astigmatism, actual CDVA values were not mentioned. For PRK Xtra, two studies (1 comparative study and 1 case series) show that it is safe in terms of CDVA (82.56% out of 109 eyes had unchanged CDVA) and safety index (0.95 [98 eyes]). The case series on SMILE Xtra for myopia showed that the procedure was safe with a calculated safety index of 1.29. However, there are few long-term reports on PRK Xtra and SMILE Xtra and more long-term studies are required to validate these results.

Complications are minimal, rare and usually transient. However, it should be noted that a case of corneal ectasia was reported 2 years post-LASIK Xtra in a hyperopic patient and a case of central toxic keratopathy was reported 3 days post-PRK Xtra in a myopic patient. The most common complication seen in combined refractive surgery and CXL is transient corneal haze, although this usually has minimal impact on visual acuity. In PRK Xtra, Sachdev et al omitted the use of MMC during the CXL process. Since the use of MMC has been shown to be efficacious in reducing the risk of corneal haze post-PRK, this omission could have contributed towards the corneal haze reported in the study. Rarer complications which have a greater impact on visual acuity such as diffuse lamellar keratitis (DLK) and central toxic keratopathy have also been reported.

Using dextran-containing riboflavin in CXL could possibly be associated with an increased risk of DLK. However, Seiler et al reported that DLK occurred in LASIK Xtra eyes even though the riboflavin used was dextran-free.

Significantly, Taneri et al reported the first case of corneal ectasia seen in the left eye after bilateral LASIK Xtra was performed on hyperopic eyes using microkeratome. This is of concern as it shows that LASIK Xtra may not be successful in its aim to eliminate the risk of iatrogenic keratectasia. However, the use of microkeratome instead of femtosecond laser in the LASIK flap creation could have contributed to the results seen. This led to an uneven thickness of LASIK flap formation which was thicker at the corneal periphery (161 µm) than at the corneal center (114 µm). A thinner residual stromal bed is a known predisposing factor for post-LASIK ectasia. However in this case, we calculated the percentage of tissue altered to be within acceptable limits at 30.4%. The central residual corneal stromal was acceptable at 390 µm. No risk factors for ectasia were present in this patient such as eye rubbing, long-term medication use, floppy eyelids, sleep apnea, family history or personal history of rigid contact lens wear. However, we noted an asymmetric bowtie pattern seen in the keratometric map of the Orbscan topography in the left eye which seems to be the only risk factor for ectasia and could possibly suggest forme fruste keratoconus. The posterior elevation map was within normal limits. Perhaps detection of subclinical corneal ectasia may be enhanced by the use of other devices such as corneal tomographic (for example Oculus Pentacam [Wetzlar, Germany]) and biomechanical devices (for example Oculus Corvis ST [Wetzlar, Germany]). These devices may be able to detect the subclinical ectasia cases. These subclinical ectasia cases should either not have any refractive surgery done or surface ablation combined with CXL could be considered.

As iatrogenic keratectasia can take anywhere from 1 week to several years after surgery to manifest, longer-term studies are needed before any conclusion about the effectiveness of LASIK Xtra in preventing iatrogenic keratectasia can be conclusively made. However, it is worrying that there has already been a case of corneal ectasia in a hyperopic patient post-LASIK Xtra, especially since hyperopic patients have a lower incidence of iatrogenic keratectasia due to preferential corneal ablation of thicker paracentral cornea in hyperopic LASIK.

UV-A energy exposure

CXL was first introduced by Wollensak, Spoerl and Seiler in the Dresden protocol with a UV-A irradiation of 3 mW/cm² for 30 minutes (5.4 J/cm²). According to the Bunsen-Roscoe Law of Reciprocity, regardless of the applied irradiance and time, the photochemical biological effect of ultraviolet light is proportional to the total energy dose delivered. Accelerated CXL techniques have been developed to shorten the time of UV-A irradiation required for CXL. UV-A irradiation in accelerated CXL varies from 7 mW/cm² in 15 minutes to 30 mW/cm² for 3 minutes while maintaining a total energy exposure of 5.4 J/cm². In combined refractive surgery and simultaneous CXL, total UV-A energy exposure varies greatly from as low as 1.4 J/cm² to as high as 5.4 J/cm². The rationale for using a lower UV-A total energy is that the indication for CXL is prophylactic rather than therapeutic and it is performed in normal and not keratoconic eyes. An additional advantage of using the accelerated protocol is reduced keratometric flattening as compared to conventional CXL. A lower total energy may reduce the number and severity of complications associated with this technique.

It is of note that complications occurred at higher total UV-A energy exposures (diffuse lamellar keratitis [Seiler et al]: 2.7 J/cm²; central toxic keratopathy [Davey et al]:...
Higher energy exposures could lead to a greater inflammatory response in the cornea which could result in DLK and central toxic keratopathy.

**Mechanisms**

It is postulated that refractive regression and iatrogenic keratectasia may have similar mechanisms – an imbalance between biomechanical stability and intraocular pressure (IOP). As refractive surgery involves the removal of corneal stromal tissue, it may reduce the biomechanical strength of the cornea, making the cornea prone to post-operative refractive and keratometric changes. Regression after the LASIK procedure may also be due to biomechanical instability and the cross-linking procedure, by improving biomechanical stability, is able to reduce the regression in both myopic and hyperopic LASIK procedures. Two comparative studies also show better keratometric stability in the LASIK Xtra group as compared to the LASIK-only group, further illustrating that CXL adds biomechanical stability to LASIK. The exact molecular mechanism of CXL is still unclear though it is postulated that CXL creates additional chemical bonds between proteoglycans, histidine, hydroxyproline, hydroxylysine, tyrosine and threonine amino-acid residues within the collagen in the corneal stroma. The formation of additional bonds between collagen fibres strengthens the cornea and could explain the increased refractive and keratometric stability. Lowering IOP with timolol eyedrops has also been found to be effective in treating LASIK patients with myopic regression, indicating that a higher IOP could be a possible factor contributing to regression.

According to 4 cohort studies, LASIK has an average retreatment rate of 12%, most of which occur within the 2 years post-LASIK. Other reports have shown a retreatment rate of up to 30% when LASIK is used to treat high myopia. Since LASIK Xtra increases refractive stability, it may reduce the need for retreatment.

Another possible explanation for reduced myopic regression rates in LASIK Xtra could be that increased epithelial hyperplasia post-LASIK results in greater myopic regression and LASIK Xtra reduces epithelial hyperplasia as compared to LASIK-only. In a study by Spadea et al. on LASIK patients with high myopia (attempted SE correction: −8.50 to −12.25D), increased epithelial thickness was found to correlate with myopic regression. Kanellopoulos et al. found that higher myopic corrections during LASIK correspond with greater post-operative epithelial thickness increase, possibly explaining the higher regression and retreatment rates seen in highly myopic patients. Additionally, Kanellopoulos et al. found that LASIK Xtra patients had less epithelial thickness increases as compared to LASIK-only patients, indicating that this could be a possible mechanism for the lower regression rates seen in LASIK Xtra.

**Patient selection criteria**

There is currently no fixed patient selection criteria or protocol for refractive surgery and simultaneous CXL. Many studies have targeted patients at high risk of regression and iatrogenic keratectasia such as those with high myopia, thin corneas, high ectasia risk score and abnormal corneal topography. Hence the current practice is to limit this procedure to high-risk patients.

**Conclusion**

Long term studies (≥1 year follow-up) show that combined refractive surgery and simultaneous CXL is effective in stabilising refractive and keratometric outcomes in patients. LASIK/PRK Xtra refractive and keratometric results are comparable to or better than the LASIK/PRK only groups. The use of LASIK Xtra has even been extended to patients with thinner corneas and higher risk of ectasia with successful results and no severe complications seen. Comparative studies have yet to be performed for SMILE Xtra, though a case series shows good safety. However, rare complications of refractive surgery and simultaneous CXL such as post-LASIK ectasia, central toxic keratopathy and DLK have been reported in recent years. Until today, no clinical study has shown that CXL prevents iatrogenic keratectasia and there has already been one report of post-LASIK ectasia seen in a LASIK Xtra patient. It should also be noted that the sample sizes used in many of the studies presented in this paper (especially studies on LASIK Xtra for hyperopia, PRK Xtra and SMILE Xtra) are relatively small and multiple studies are often carried out by the same few authors. Hence it may be difficult to make conclusions on this subject. Future studies, especially randomised long-term comparative studies, would be useful in further evaluating safety and efficacy of these procedures. More research should also be performed to optimise UV-A irradiation settings to potentially reduce the incidence and severity of complications without compromising efficacy.

**Declaration**

LL has received travel reimbursement and honourarium from Avedro in the past 1 year. Otherwise, the authors did not receive any sources of public or private financial support. The authors do not have any financial or proprietary interests in any product, material or method.

**Funding**

The authors did not receive any sources of public or private financial support. The authors do not have any financial or proprietary interests in any product, material or method.

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