CORNEAL COLLAGEN CROSS-LINKING – CLINICAL OUTCOMES AND THE EVOLUTION OF FIVE YEARS OF PUBLIC SERVICE IN AUCKLAND

Ocular Therapeutics Conference 2020

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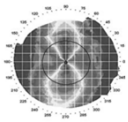
No Financial Disclosures

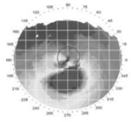
nz national eye centre | The University of Auckland New Zealand | Medical and Health Sciences

KERATOCONUS

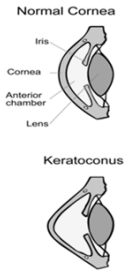
Simulation of what someone with keratoconus perceives



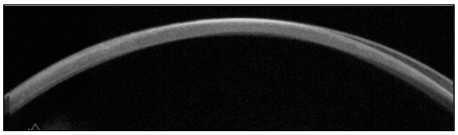
Regular Astigmatism – "Normal"



Irregular Astigmatism – Keratoconus



KERATOCONUS VS. NORMAL



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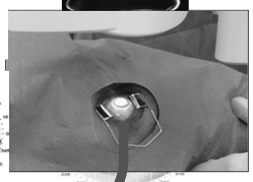
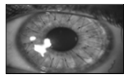
- Deformation amplitude higher in keratoconus

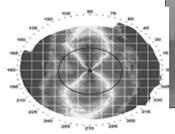
Keratoconus - Treatment

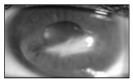
Basic treatment algorithm as disease progresses:

spectacles ⇨ contact lenses ⇨ transplantation









2009-2012

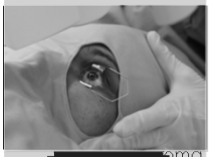
- Dr Charlotte Jordan's PhD
- Randomised control trial
- Traditional CXL protocol
- 39 patients
  - Traditional CXL safe and effective

Identifying, Characterising and Modifying the Natural History and Progression of Keratoconus in New Zealand/ Aotearoa

Charlotte Ann Jordan

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Department of Ophthalmology, The University of Auckland, 2012.

TRADITIONAL CORNEAL CROSS-LINKING



Endothel… …oma

Stroma soaked in riboflavin (vitamin B2) for 30 minutes

Expose to continuous/uninterrupted ultraviolet light of 3mW/cm^2 for 30 minutes = total energy of 5.4 J/cm^2

2014-2016

- Dr Akilesh Gokul's PhD
- High intensity, high energy continuous vs. pulsed UV-A CXL
  - High energy accelerated cxl
- Randomised intervention study
- 80 eyes with 2 year follow-up
  - 40 eyes/group

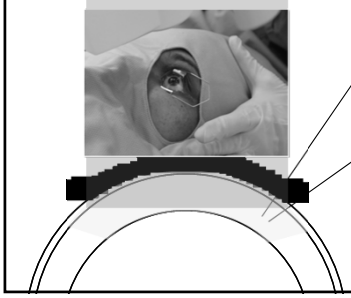

Characterising and Modifying the Keratoconus Disease Process in New Zealand – The Aotearoa Research into Keratoconus (ARK) Project

Akilesh Gokul

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Ophthalmology

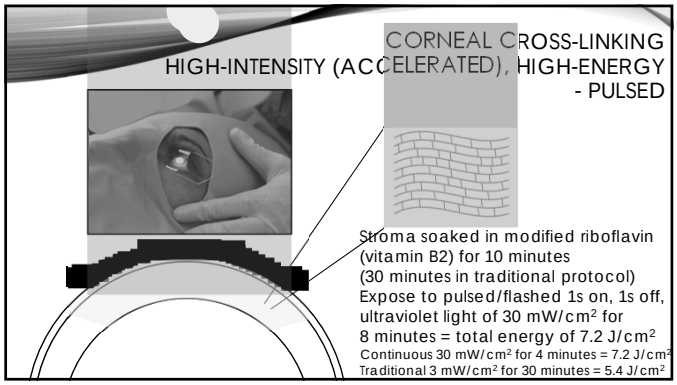
The University of Auckland, 2017

CORNEAL CROSS-LINKING HIGH-INTENSITY (ACCELERATED), HIGH-ENERGY - CONTINUOUS



Stroma soaked in modified riboflavin (vitamin B2) for 10 minutes
(30 minutes in traditional protocol)
Expose to continuous/uninterrupted ultraviolet light of 30 mW/cm^2 for
4 minutes = total energy of 7.2 J/cm^2
(vs. 3 mW/cm^2 for 30 minutes = 5.4 J/cm^2)

CORNEAL CROSS-LINKING HIGH-INTENSITY (ACCELERATED), HIGH-ENERGY - PULSED



Stroma soaked in modified riboflavin
(vitamin B2) for 10 minutes
(30 minutes in traditional protocol)
Expose to pulsed/flashed 1s on, 1s off, ultraviolet light of 30 mW/cm^2 for
8 minutes = total energy of 7.2 J/cm^2
Continuous 30 mW/cm^2 for 4 minutes = 7.2 J/cm^2
Traditional 3 mW/cm^2 for 30 minutes = 5.4 J/cm^2

WHY CONTINUOUS VS. PULSED?

- Cross-linking: UV-A + Riboflavin = Reactive Oxygen (O_2) Species
- Reactive O_2 species = ↑ covalent bonds[1]
- Type I and II photodynamic reaction[1]
  - Type II more efficient but oxygen dependent
- O_2 in cornea depleted rapidly on UV-A initiation[2]
  - 30mW/cm^2 ↓ zero in 1s, 3 mW/cm^2 takes 15s
- O_2 concentration rapidly increases once UV-A stopped[2]
  - Theoretically pulsing UV-A = ↑ Type II reaction = ↑ covalent bonds

1. Spoerl E, Seiler T. Techniques for stiffening the cornea. J Refract Surg 1999;15:711-713.
2. Kamaev P, Friedman MD, Sherr E, et al. Photochemical kinetics of corneal cross-linking with riboflavin. Invest Ophthalmol Vis Sci 2012;53:2360-2367.

SUMMARY OF KEY RESULTS[1]

- At 24 months follow-up compared to baseline:
- No significant difference in UVA, K_{Mean} and CTP in both p-ACXL and c-ACXL
- CDVA improved significantly in both p-ACXL and c-ACXL
- MRSE improved significantly and K_{MAX} decreased significantly in the c-ACXL group only
- No complications encountered in either group

1. Ziaei, M., **Gokul, A.,** Meyer, J. J., Vellara, H. R., Patel, D. V., & McGhee, C. N. **(2019)** Prospective Two Year Study of Clinical Outcomes Following Epithelium-off Pulsed versus Continuous Accelerated Corneal Crosslinking for Keratoconus. Clinical and Experimental Ophthalmology. 47(8):980-986.

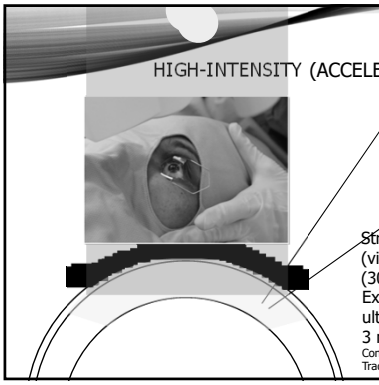
CONCLUSION

- Both pulsed-ACXL and continuous-ACXL safe and effective at halting the progression of keratoconus at 24 month follow-up
- Continuous-ACXL may offer superior refractive and tomographic outcomes but may not translate into better visual outcomes
- Continuous possibly the superior method due to shorter procedure time i.e. more efficient – 5 pulsed = 6 continuous

2016-2020

- ADHB service
- Continuous UV-A Accelerated CXL
  - Different protocol to Dr Jordan's and Dr Gokul's PhDs
  - 10 minute riboflavin soak
  - 3 minute continuous UV-A exposure
    - 30mW/cm^2 for 3 minutes = total energy of 5.4 J/cm^2
    - High intensity, traditional energy
- Weekly list
  - ~160 procedures per year

CORNEAL CROSS-LINKING
HIGH-INTENSITY (ACCELERATED), TRADITIONAL-ENERGY - CONTINUOUS



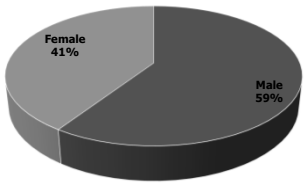
Stroma soaked in modified riboflavin (vitamin B2) for 10 minutes
(30 minutes in traditional protocol)
Expose to continuous/uninterrupted ultraviolet light of 30 mW/cm^2 for
3 minutes = total energy of 5.4 J/cm^2
Continuous high energy 30 mW/cm^2 for 4 minutes = 7.2 J/cm^2
Traditional 3 mW/cm^2 for 30 minutes = 5.4 J/cm^2

POST-OP CARE

- Bandage CL placed
- Ciloxan QID for 1 week, Fluoromethalone QID for 1 month
- Review 3 days post
  - Remove bandage CL – most epithelial defects almost fully healed
- Review 6 weeks, 3 months, 6 months and 1 year post-op
  - Then on case-by-case basis -> 3-12 monthly
- Encouraged to see optometrist for spectacle and/or CL review after 3 month post-op visit

WHO IS UNDERGOING CXL?
NUMBER OF PROCEDURES AND GENDER

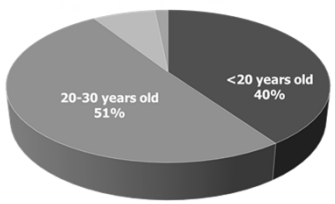
- Total number procedures = 573 eyes of 426 patients
  - 500 epi-off
  - 73 transepithelial[1]
    - 2014-2016 = 53 (72.6%)
    - 2017-2020 = 20 (27.4%)
- Gender



1. Ziaei, M., **Gokul, A.,** Vellara, H. R., Patel, D. V., & McGhee, C. N. **(2019).** Prospective 2-year study of accelerated pulsed transepithelial corneal crosslinking outcomes for Keratoconus. *Eye (Lond)*: 1897-1903.

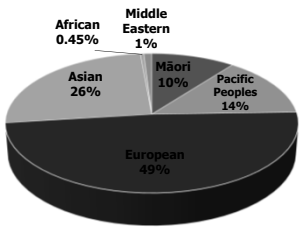
WHO IS UNDERGOING CXL?
AGE

Mean age on the day of CXL - 22.41 ± 6.75 years (range 7-48)

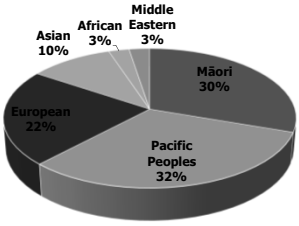


WHO IS UNDERGOING CXL?
ETHNICITY

Auckland Region*



CXL - ADHB



*2018 census

CRITERIA FOR PROGRESSION

- At least 6 months of visual/refractive/ tomographic data available
- Progression defined as ≥one of:
  - Increase in maximal keratometry of ≥0.75D
  - Change in refractive astigmatism of ≥0.75D
  - Decrease in thinnest corneal thickness of ≥15µm
  - Progression measured indirectly by using rigid contact lenses; a change of >0.2mm in base curve
  - Loss of 2 or more lines of best spectacle corrected visual acuity
- Clinician judgement

SAFETY LIMITATIONS

- Corneal thickness
  - Thinnest point >400 µm
- Corneal clarity
  - No significant corneal scarring -> from KC or otherwise
- Inflammatory disease under control -> non-healing epithelial defects
  - E.g. allergic eye disease (VKC, AKC, SAC)
- No limitation on keratometry values
  - As long as above criteria are met

CLINICAL OUTCOMES SINCE 2014

- 5 (1%) infections
  - All admitted for fortified topical antibiotics
  - No loss of BCVA
- 8 (1.4%) repeat CXL procedures
  - 3 initially had transepithelial CXL
- Zero eyes that have had epi-off CXL progressed to transplant
  - 1 patient that had transepithelial CXL progressed to hydrops
- Many patients change in spec and CL Rx

SO WHAT ARE THE RISKS?

- 0.5-1% infection risk
- ~1% failure – require repeat procedure (if possible)
- Possible spectacle or CL Rx will change
  - Even without complication
  - Advised to not update for at least 3 months post-op
- Unaided vision can change even without complication
  - Depending on what happens to spec/CL Rx

SUMMARY

- CXL has evolved substantially over the last decade in Auckland
  - Current protocol is accelerated CXL with continuous UV-A
- Procedure routinely carried out
  - Weekly list
- Main risk is infection (0.5-1%)
- Early disease detection remains a challenge
  - Mostly individuals aged 20-30 (~50%) undergoing CXL
- Very large ethnic bias
  - 30% Māori
  - 32% Pacific Peoples
  - 22% European

ACKNOWLEDGEMENTS

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- Prof Dipika Patel
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- Dr Hans Vellara
- Dr Jay Meyer
- Dr Stuti Misra

- University of Auckland Doctoral Scholarship
- NZAO Post-Graduate Scholarship
- NZAO Post-Doctoral Fellowship

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