

The author has no financial interests or relationships to disclose

RCT Results of Perceptual Amblyopia Therapy for Improving Vision & Contrast Sensitivity Functions in Crosslinked Stable Keratoconus

Poster # 99713

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 **ASCRS**
ANNUAL MEETING
APRIL 5-8, 2024 | BOSTON, MA

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Origin of the Concept

- Neural mechanisms are the basis for loss of spatial and binocular vision in amblyopia, and that a degree of neural plasticity persists well beyond the sensitive period.
- Perceptual learning, video game play and binocular methods aims at reducing inhibition of the amblyopic eye by the strong fellow eye, and enhancing binocular fusion and stereopsis ¹
- **Lunghi C et al.**, suggested a non invasive training strategy for adult human amblyopia based on an inverse-occlusion procedure combined with physical exercise ²
- **Paudel N.**, reviewed games for amblyopia that are commercially available in mobile applications ³

The Visual Perceptual Therapy is interactive web-based computer software that provides a series of individualized visual stimuli, which are designed to enhance the neural interactions in the visual cortex.

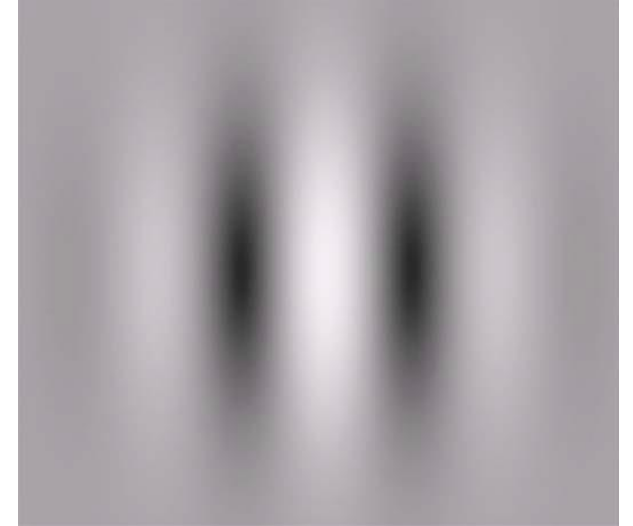
While Keratconus treatments are effective in slowing and stopping the progression of the disease, it does not typically restore vision and patients are left with poor best corrected vision.

Reference:

1. Levi DM. Rethinking amblyopia 2020. Vision research. 2020 Nov 1;176:118-29.
2. Lunghi C, Sframeli AT, Lepri A, Lepri M, Lisi D, Sale A, Morrone MC. A new counterintuitive training for adult amblyopia. Annals of clinical and translational neurology. 2019 Feb;6(2):274-84.
3. Paudel N. Smartphone applications for amblyopia treatment: a review of current apps and professional involvement. Telemedicine and e-Health. 2018 Oct 1;24(10):797-802.

Visual Perceptual Therapy Program - Overview

- The basic element of visual stimulation is the Gabor Patch.
- It matches the shape and orientation of the primitive receptive fields of neurons in the primary visual cortex and therefore effectively activates them.
- The goal of the 2 computerized evaluation (CE) sessions is to identify cortical functional deficits, which enable the software to tailor an individual computerized training regime to match patient specific needs.
- This is done by measuring patient's vision threshold in different types of visual tasks.
- Neurons in the primary visual cortex are selective for the size, orientation and direction of motion of patterns falling within a restricted region of visual space known as the receptive field.
- The software analyzes the contrast threshold of a Gabor target with the presence of 2 flankers Gabor.
- The patient is exposed to two short displays in succession and the patient identifies which display contains three Gabors.
- The exercise becomes harder until a point where the patient can't see the target Gabor and can't identify the correct display from the 2 options and makes a mistake.



STUDY OBJECTIVES:

To evaluate computer based perceptual visual therapy regime using Gabor patches for improving visual acuity and contrast sensitivity function (CSF) in crosslinked stable keratoconic eyes

Sample Size :

30 subjects randomized in 2:1 ratio into treatment and control arms.

Trial Registration :

Clinical Trial Registry of India- CTRI/2022/09/045779

Study Outcomes:

Percentage of patients improving distance BCVA by at least 2 lines at study end in comparison to baseline.

Improvement in Contrast Sensitivity scores.

STUDY DESIGN

A Randomized, Parallel Group, Active Controlled Trial

INTERVENTIONAL ARM: (N = 20)

- Screening -1 to -8 weeks
- Visual training treatment for 12-14 weeks
- Follow-up in week 26 and week 50

CONTROL ARM: (N=10)

- Controlled arm with out a interactive web-based computer software training
- 10 patients with out a interactive web-based computer software training will serve as a controlled arm.
- Screening -1 to -8 weeks
- No Visual training treatment for 12-14 weeks
- Follow-up in week 26 and week 50

VISUAL PERCEPTUAL THERAPY – Mechanism of Action

Development of a more efficient and effective neural processing, by targeting specific cortical deficits and enhancing specific neural response and creating new neural connections at the synapse level through a perceptual learning technique.

Methodology

- Each training session lasts for approx. 30 minutes during which the patient needs to respond to visual perception tasks (VPTs) displayed on the computer screen.
- During a session, the patient sits 1.5 meter away from the computer monitor in a darkened room and a mouse is used to respond to the tasks.
- Patients perform the training session with best optical correction and while the dominant eye is blurred with a semi-transparent milky cover, and while keeping the dominant eye open underneath the cover.

Screening period:

- After informed consent signing, patients' eligibility was assessed with two Computerized Evaluation (CE) training sessions.
- Patients who eligible for the study underwent BCVA distance & near and CSF baseline measurements and corneal topography.
- In case two computerized evaluation sessions were not sufficient, 8 more computerize evaluation sessions were conducted by the patients at home.

Inclusion Criteria

1. Man & woman 14-55 years old, who is diagnosed with post-CXL stable keratoconus, by serial Topographic and clinical analysis.
2. Stable keratoconus parameters including Kmax, Ksteep, astigmatism and corneal thickness in the past 12 months.
3. Stable BCVA for 12 months.
4. Willing to practice 3-4 times per week x 30 minutes each training, for 12 consecutive weeks.
5. BCVA between 6/9 to 6/30 inclusive, using ETDRS VA test chart prior or during the screening visit.
6. Subject with Contrast Sensitivity Function below-normal range, measured in FACT sine wave test chart during screening visit.
7. Subject pass successfully Computerized Evaluation 1 and 2 as defined by the system.

Exclusion Criteria

1. CXL within 12 months
2. Severe untreated attention disorder.
3. Chronic migraines based on subject self-reporting.
4. Subject who diagnosed with Epilepsy.
5. Other ocular disease beside keratoconus.
6. Behavioral or neurological disorders which may interfere with the study

Visual perceptual Therapy period

- Patients were randomized to the study and control arm and underwent Visual perceptual Therapy period till 12 weeks at patients' home.
- Each patient performed a total of 40 ± 5 times the Visual perceptual Therapy sessions during the course study.
- Patients required to perform the computerized training sessions 3 to 4 times a week, approximately 30 minute each session.
- In this period, one periodic exam of BCVA and CSF(6 weeks after randomization).
- Termination visit End of Visual perceptual Therapy therapy period: 12weeks.

Optical Correction

- Subjects were wearing best optical correction all day during the 10-12.5 months study period.
- Subjected to the optical correction before starting the study.
- Up to 3.5 diopters anisometropia – subjects were allowed to use glasses or contact lenses.
- If anisometropia is higher than 3.5 diopter, subjects were corrected with contact lenses only.

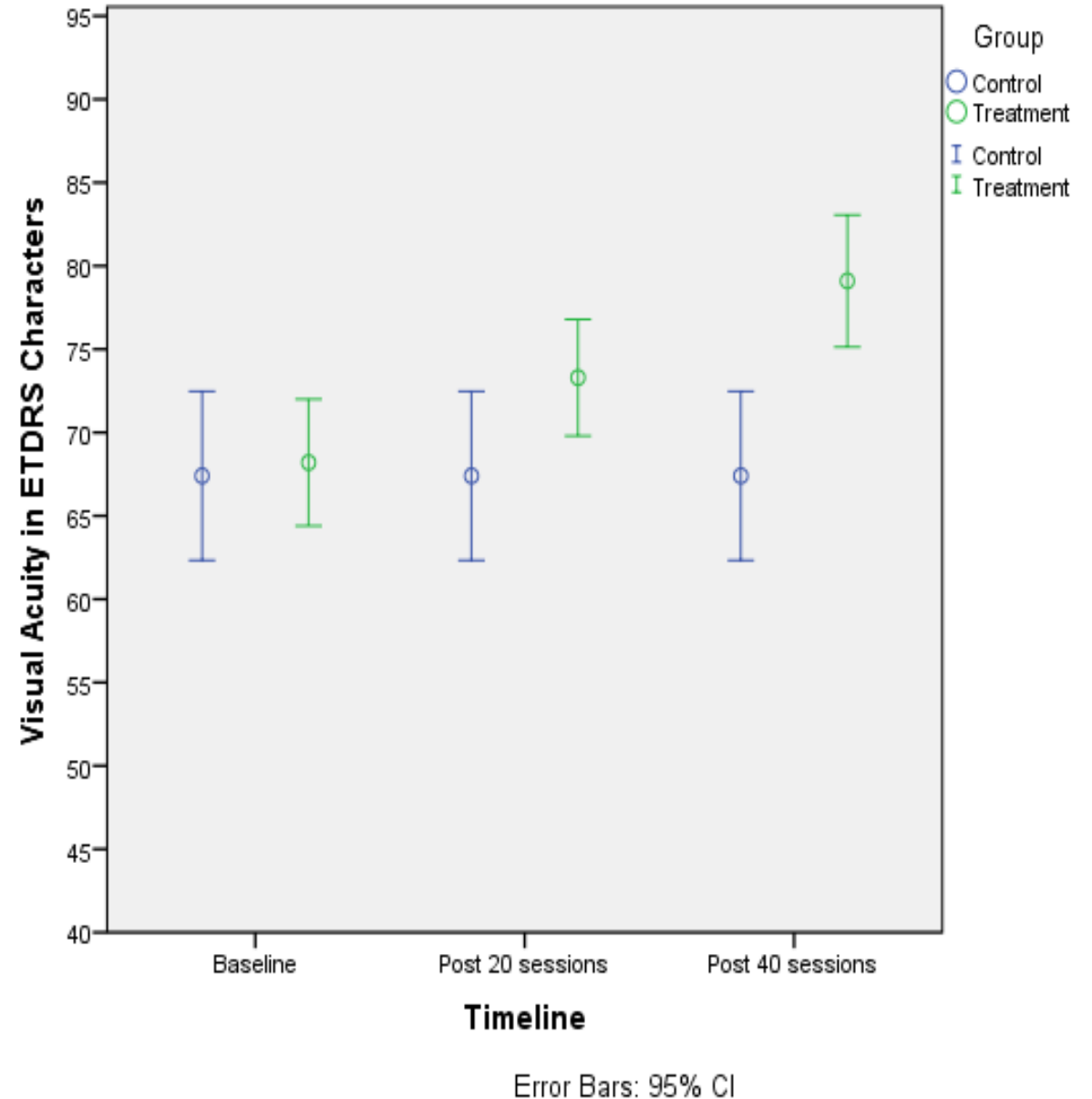
Visual Perceptual Therapy Sessions

- During each treatment session, the subjects were exposed to visual images displayed on a computer monitor.
- Subjects were exposed to two consecutive displays in random order.
- Each display has some arrangement of Gabor patches with subtle difference between the two displays.
- A special algorithm analyzes the results, and sends back to patient computer the next training session, tailored to patient's progress and needs.
- Subjects who failed to pass one of the computerized evaluation (CE) sessions after a total of 10 CE sessions, was removed from the study as screening failure.
- In case two computerized evaluation sessions were not sufficient, up to 8 more computerized evaluation sessions were conducted

Results - Visual Acuity (in ETDRS)

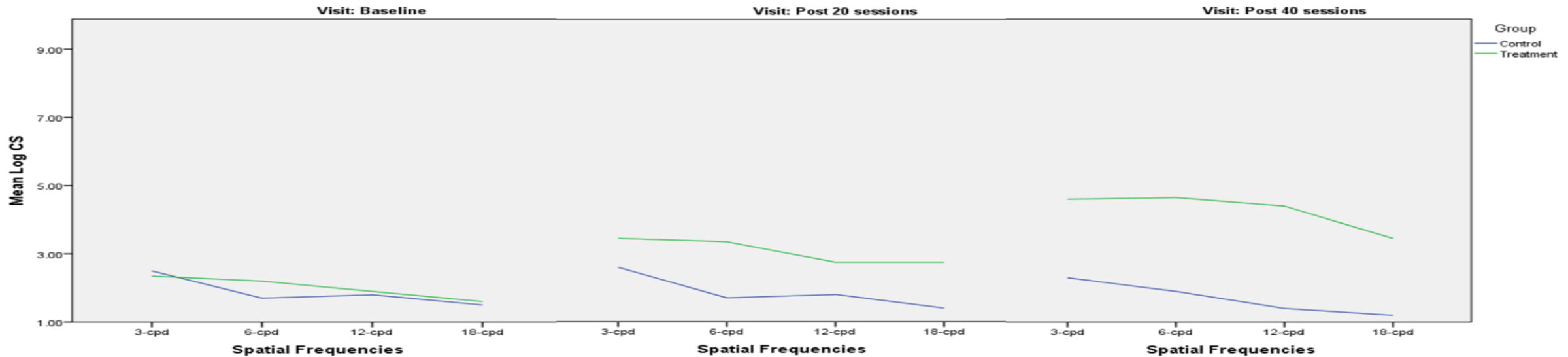
S. No	Group	Screening		Post 20 Session		Post 40 Session		P Value (ANOVA)
		VA		VA		VA		
		Mean	SD	Mean	SD	Mean	SD	
1	Control	67.40	7.09	67.91	6.53	67.65	8.31	0.875
2	Treatment	68.20	8.11	73.30	7.48	79.10	8.47	<0.0001

85% of subjects in the treatment arm had 2 or more Snellen's lines improvement in vision after 40 sessions



Contrast Sensitivity Function

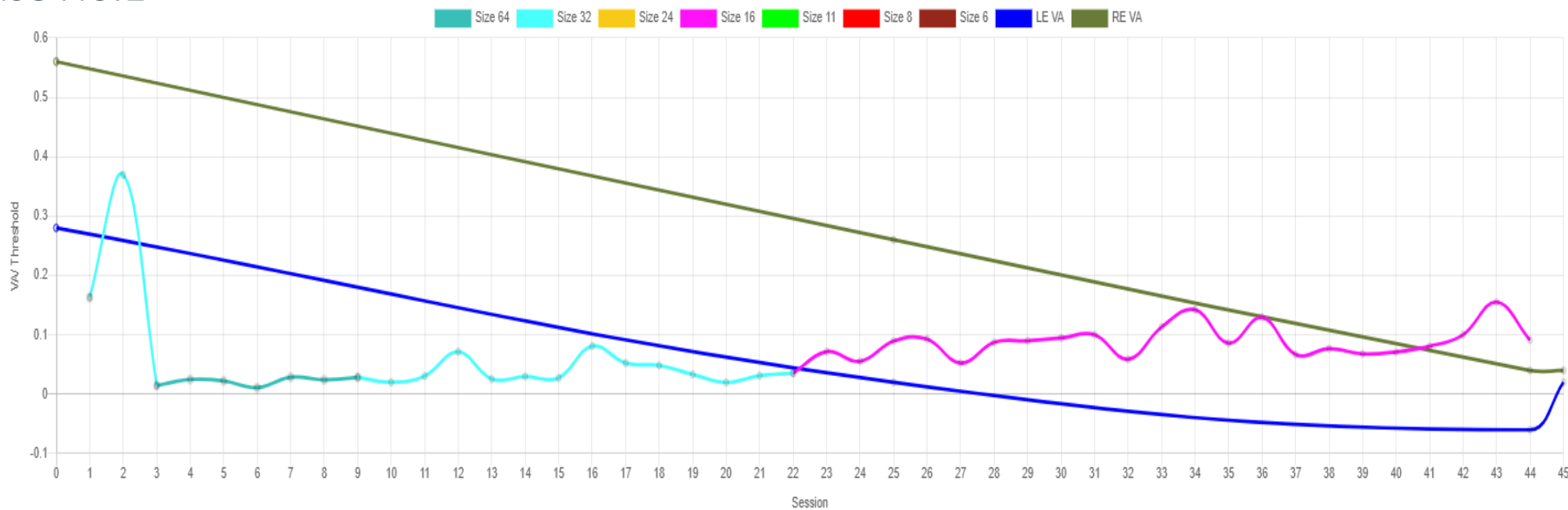
S. No	Group	Screening								Post 20 Session								Post 40 Session							
		CS3cpd		CS6cpd		CS12cpd		CS18cpd		CS3cpd		CS6cpd		CS12cpd		CS18cpd		CS3cpd		CS6cpd		CS12cpd		CS18cpd	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	CONTROL	2.50	1.18	1.70	1.16	1.80	0.79	1.50	0.71	2.60	1.07	1.70	1.16	1.80	0.79	1.40	0.52	2.30	1.33	1.90	1.10	1.40	0.70	1.20	0.63
2	TREATMENT	2.35	1.22	2.20	1.32	1.90	1.25	1.60	1.23	3.45	1.31	3.35	1.39	2.75	1.16	2.75	1.21	4.60	1.47	4.65	1.81	4.40	1.81	3.45	1.70



CSF improved significantly in the treatment arm at all spatial frequencies

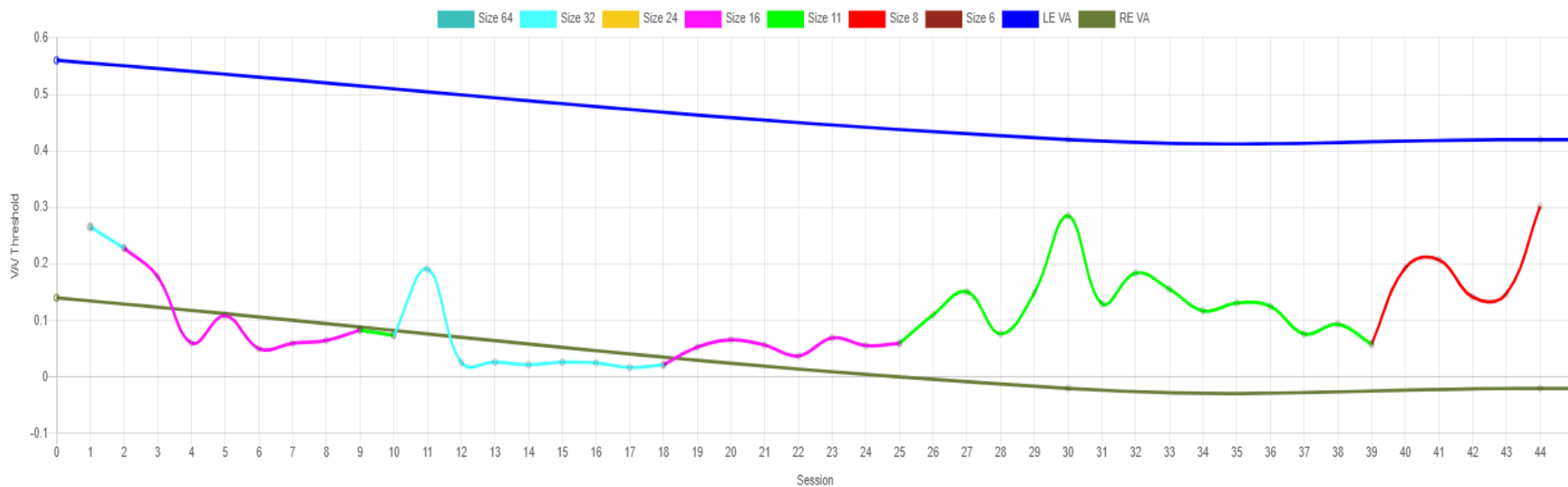
Representative graphs showing improved vision of the study eyes (RE) in two subjects

Case No.1



Timeline	LE VA (LogMar)	RE VA (LogMar)
Baseline	0.28	0.56
Post Session 20	0.02	0.26
Post Session 40	-0.06	0.04
Post Treatment	0.02	0.04

Case No.2



Timeline	LE VA (LogMar)	RE VA (LogMar)
Baseline	0.56	0.14
Post Session 20	0.42	-0.02
Post Session 40	0.42	-0.02
Post Treatment	0.42	-0.02

What is known of amblyopia:

- A binocular approach to treating anisometropic and strabismic amblyopia has recently been advocated in current practice
- In children aged 5 - 13 years, amblyopic-eye VA improved with binocular game play and with patching, particularly in younger children (5 to 7 years) without prior amblyopia treatment ¹
- Holmes JM compared visual acuity (VA) improvement in children aged 7 to 12 years who have received previous treatment for amblyopia other than spectacles. There was no benefit to VA or stereoacuity from 4 or 8 weeks of treatment with the dichoptic binocular Dig Rush iPad game ² Binocular games that rebalance contrast to overcome suppression are a promising additional option for treating amblyopia.
- Gao TY et al ³ compared the effectiveness of a binocular video game with a placebo video game for improving visual functions in older children and adults. Suggested more engaging video games with considerations for compliance may improve effectiveness.

What this paper add:

- Visual perceptual Therapy trains brain to see better without additional surgery, enhancements, drugs or side effects.
- Subjects have experienced improved eye sight and quality of vision.
- Keratoconus subjects, post stabilization by CXL on an average, improved their visual acuity by more than two lines on ETDRS chart and increased their contrast sensitivity more than 50% from baseline visit to end of the study visit.
- We also found statistically significant improvement in VA and CSF in comparison to control arm in keratoconus subjects.

References:

1. Holmes JM, Manh VM, Lazar EL, Beck RW, Birch EE, Kraker RT, Crouch ER, Erzurum SA, Khuddus N, Summers AI, Wallace DK. Effect of a binocular iPad game vs part-time patching in children aged 5 to 12 years with amblyopia: a randomized clinical trial. *JAMA ophthalmology*. 2016 Dec 1;134(12):1391-400.
2. Holmes JM, Manny RE, Lazar EL, Birch EE, Kelly KR, Summers AI, Martinson SR, Raghuram A, Colburn JD, Law C, Marsh JD. A randomized trial of binocular dig rush game treatment for amblyopia in children aged 7 to 12 years. *Ophthalmology*. 2019 Mar 1;126(3):456-66.
3. Gao TY, Guo CX, Babu RJ, Black JM, Bobier WR, Chakraborty A, Dai S, Hess RF, Jenkins M, Jiang Y, Kearns LS. Effectiveness of a binocular video game vs placebo video game for improving visual functions in older children, teenagers, and adults with amblyopia: a randomized clinical trial. *JAMA ophthalmology*. 2018 Feb 1;136(2):172-81.

Fiedman tests for repeated measures showed no statistical differences between study visits with the p values of 0.097, 0.135, 0.05 and 0.097 for 3cpd, 6cpd, 12cpd and 18cpd respectively in CONTROL arm, whereas TREATMENT arm had statistically significant difference ($p < 0.0001$) in CSF between study visits in all spatial frequencies.

CONCLUSIONS

- Sequential, patient specific, perceptual learning program based on visual stimulation improved vision and contrast sensitivity in crosslinked keratoconus with visual deficiencies & acts as a proof of concept of improving neural connections at cortical level.
- Keratorefractive surgeons could consider this as a post operative therapeutic adjuvant as a 'BETTER TOGETHER" concept in all crosslinked corneas.