Patient specific determination of change in ocular spherical aberration to improve near and intermediate visual acuity in presbyopic eyes

Short title: Adaptive optics visual simulation for presbyopia

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Abstract

The purpose was to determine the optimum negative spherical aberration induction required to improve near and intermediate visual acuity (VA) of presbyopic eyes. A total of 174 normal and diabetic (no retinopathy) presbyopic eyes (age ≥ 40) were measured with Visual adaptive optics simulator (Voptica, Spain). First, baseline uncorrected VA and aberrations were measured. VA at

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40 cm (near), 80 cm (intermediate) and distance was measured. Then, a negative spherical aberration (SA) was added to baseline ocular SA and VA at all targets was reassessed after correction of distance refractive error. Clinically, baseline SA and root mean square of higher order aberrations were similar between the normal and diabetic presbyopic eyes. Baseline VA of the diabetic eyes at near and intermediate was better than the same of normal eyes (p=0.001). After SA change, VA at near and intermediate of both normal and diabetic presbyopic eyes improved. However, fewer diabetic eyes needed higher SA change than normal eyes (p=0.03). The corresponding trends with change in VA at near and intermediate were also similar between the normal and diabetic eyes. Patient specific modulation of ocular SA to improve near and intermediate VA in a large cohort of eyes was successful in improving VA, sometimes even distance VA.

Introduction

Accommodation is a unique feature of the eye that allows it to focus distant, intermediate and near objects. The key modulators of accommodation include the lens shape, lens refractive index and pupil diameter.[1] In younger normal eyes, axial lens thickness, cortical thickness and nuclear size generally increased with age.[2] However, the front radius of curvature, back radius of

curvature and anterior chamber depth decreased with age.[2] These trends were enhanced by 52% to 121%, if the subject had an early (age less than 30 years) onset of diabetes and clear lens.[2] In patients with late onset of diabetes, the differences between normal and disease eye lenses were less significant.[3] This indicated that both age and duration of diabetes, if known, played a significant role in lens biometry.[3] Thus, the accommodative power of diabetic eyes, with no diabetic retinopathy, could be different from that of normal eyes, depending on the onset of the diabetes.

Since the human lens became more convex with age, the eye generally became myopic. However, a recent study showed that a paradoxical decrease in lens refractive index compensated for the increase in convexity of the lens with age in both normal and diabetic eyes.[1] Further, the decrease was more in patients with diabetes type 1 than in patients with diabetes type 2.[1] Thus, normal and diabetes type 2 eyes could have similar accommodative performance, when matched with age, clear lens and media. This hypothesis was supported by a recent study where accommodative amplitudes of diabetes type 1 eyes, with no or very mild diabetic retinopathy, were lower than the normal eyes.[4] Another interesting feature of accommodation is the natural change in spherical aberration (SA) of the eye from positive to negative in both young and old eyes.[5] In older eyes, this change in SA could be lower due to stiffer lens and resulting lower accommodation amplitude.[2,6,7] Thus, decrease in ocular SA could be a possible solution to expand the depth of focus in presbyopic eyes, both in normal and disease eyes.[8] However, the magnitude of SA change required could vary between patients and may also be determined by diabetes[4]. Therefore, the aim of this study was to investigate the performance of individual eyes at near (40 cm), intermediate (80 cm) and distance reading targets by precise modulation of the

in situ SA of the eye using a novel adaptive optics vision simulator[9,10] in normal and diabetic patients above the age of 40. A threshold value of change in SA was determined to achieve maximum improvement in near and intermediate visual acuity without a severe drop in distance visual acuity. The age of 40 was chosen as the lower limit since early presbyopia effects were found in patients at and above the age of 40 years usually.

Methods

This was a prospective, observational, cross-sectional study conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent. The study was approved by the ethics committee of the Narayana Nethralaya eye hospital, Bangalore. A total of 174 eyes of 174 healthy individuals were recruited from patients visiting the general out-patient department of the hospital over a period of six months. Participants with spherical correction less than ±4.00 Diopters (D) and astigmatism less than 2.00 D were included. Additionally, 73 eyes of 73 Type 2 diabetic patients with clear ocular media, no diabetic retinopathy, no previous ocular surgery, age above 40 years, astigmatism lower than 2D, and monocular uncorrected distance visual acuity better than 0.2 were included. Clear ocular media was assessed with indirect ophthalmoscopy.[11] Exclusion criteria included the presence of progressive myopia, advanced keratoconus, active ocular disease, diabetic retinopathy, contact lens wear or any other ocular diagnosis that may alter the optical quality. All the subjects underwent complete ocular examination with slit-lamp examination and fundus evaluation. All diabetic patients underwent dilated optical coherence tomography imaging (1050 nm swept-source OCT) after vision simulation to rule out diabetic retinopathy in the central and peripheral retina (DRI Triton Plus, Topcon Inc., Japan).

Vision assessment and simulation was performed in non-dilated eyes with Visual adaptive optics simulator (VAO, Voptica Inc., Murcia, Spain). VAO has a Shack-Hartman sensor to measure the ocular wavefront aberrations.[12] It also has a liquid crystal spatial light modulator to modify the measured aberrations and perform objective vision testing at different target distances within a fixed measurement and evaluation diameter of 4.5 mm.[12] If the pupil diameter of the patient was greater than 4.5 mm, VAO would restrict the measurement to only 4.5 mm in diameter. The following was the protocol used to assess accommodation in normal and diabetic eyes:

a) Three repeat measurements of the ocular wavefront aberration were obtained. Aberrations were quantified with Zernike polynomials up to order 6 with *in situ* pupil diameter. The average of the Zernike coefficients was calculated. The lower order aberrations were converted to distance sphere and cylindrical refractive error.
b) Then, the patient was subjected to visual acuity (VA) assessment. The patient was asked to read the letters on the Snellen's chart through the device view finder. Uncorrected VA was measured at different *in built* reading targets in the following order: distance, 80 cm (intermediate) and 40 cm (near).
c) Then, only the SA of the measured wavefront was modulated in steps of –0.05 μm and VA was retested at different reading targets in the same order as in (b). For both (b) and (c), pupil diameter was recorded. Prior to SA modulation, distance refractive error [determined from step (a)] was corrected.
d) Each incremental SA (ΔSA) resulted in progressive worsening of distance VA but progressive improvement in intermediate and near VA, generally. However, there was a

threshold value of ΔSA beyond which the intermediate and near VA also began to worsen. For each eye, this threshold value (ΔSA_T) was recorded. ΔSA_T was converted to an equivalent spherical correction (ΔD in Diopters) using the following formula[13]:

$$\Delta SA_D = \frac{12\sqrt{5}}{R^2}\Delta SA_T \quad \text{.....(1)}$$

where R was equal to 2.25 mm or radius of measurement zones of VAO. The equivalent spherical correction allowed to calculate the net effect (or interaction) of different aberrations into an equivalent lower order (sphere [ΔSA_D] and cylinder) change[13]. Since SA is a symmetrical aberration and was the only parameter modified, theoretically it left the cylinder unchanged.

The aberration measurement and VA testing was conducted under mesopic external lighting condition to avoid any stray light from entering the eye.

Statistical analyses

All continuous variables were assessed for normality of distribution with Kolmogorov-Smirnov test. Since some of the variables were non-parametric, median [minimum-maximum] was used. Friedman test was used to compare the variables before and after modification with ΔSA_T within a group (normal and diabetic eyes). Kruskal-Wallis test was used to compare parameters between the normal and diabetic eyes group. MedCalc v17.6 (MedCalc Inc., Belgium) was used for all statistical analyses.

Results

The median age of normal and diabetic eyes were 45 [39, 66] and 47 [40, 67] years, respectively (p=0.01). The median duration of diabetes from the time of first diagnosis was 3 [1,14] years, respectively. Tables 1 and 2 list the demographics of normal and diabetic eyes along with study outcomes. In Table 2, all VA's are reported as decimal. Spherical refractive error (Table 1) was similar between the two groups (0.0 [–4, 2.5] vs. 0.0 [–1.5, 1.5]; p=0.12). Cylinder was significantly higher in the diabetic eyes than the normal eyes (p=0.02), though this difference wasn't clinically significant (Table 1). Root mean square of higher order ocular aberrations (HOA_{rms}, Table 1) was marginally greater in the diabetic eyes (p=0.04). Baseline (i.e. before induction of ΔSA_T) SA of normal and diabetic eyes were similar (p=0.44, Table 2). Interestingly (Table 2), baseline uncorrected VA at 40 cm and 80 cm were significantly inferior in the normal eyes than the diabetic eyes (p<0.001). However, baseline VA for distance vision (Table 2) was the same between the two groups (p=0.87).

From Table 2, the ΔSA_T appeared similar between the normal (-0.15 µm [0,-0.3]) and diabetic (-0.15 µm [0,-0.3]) eyes. However, the two groups were statistically different (p=0.03). The equivalent change in Diopters also demonstrated the same significance (p=0.03). The % distribution of eyes in ΔSA_T (Diopters) among the normal presbyopes was 23%, 28.2%, 20.1% and 28.7%, respectively for 0 to <0.4 D, 0.4D to <0.8D, 0.8D to <1.2D and 1.2D to <1.6D, respectively. Among the diabetic eyes, the same was 31.5%, 35.6%, 11%, and 21.9%, respectively. Thus, this difference in % distribution was responsible for the statistical significance of ΔSA_T (Diopters) and ΔSA_T (µm) between normal and diabetic eyes (Figure 1). The median improvement in VA at 40 and 80 cm (Table 2) were different between the groups (p=0.001). Figure 2 shows a dot plot of ΔSA_T, change in VA at near, intermediate and distance

reading targets for the normal and diabetic eyes. However, the % distribution of improvement in VA of the diabetic eyes was lower since these eyes already had better baseline VA at 40 and 80 cm before induction of ΔSA_T. The % distribution of change in VA was the same as obtained for ΔSA_T (Diopters) and ΔSA_T (µm). Baseline pupil diameter differed between the groups (p=0.032) and the difference was maintained (p=0.001) after ΔSA_T (µm) was induced (Table 1). Duration of diabetes had no correlation with any of the VA parameters (p>0.05).

Discussion

In this study, the accommodative power of patients eyes above the age of 40 and systemically affected by diabetes was investigated using a novel adaptive optics visual simulator via modulation of ocular SA. In normal eyes above age 40, VA at 40 cm and 80 cm were affected naturally due to presbyopia (Table 1). By inducing ΔSA_T, VA at 40 cm and 80 cm for most eyes improved significantly. From Table 2, several eyes also noted a significant increase in visual acuity even at distance after ΔSA_T, e.g. maximum increase in VA at distance was 0.35. Interestingly, VA of the diabetic eyes at 40 cm and 80 cm were better than the normal eyes at baseline. ΔSA_T again led to an improvement in their near vision and in some eyes even in their distance vision (Table 1). These trends haven't been reported in literature before and have important implications for correction of presbyopia either with surgical ablation or with lenses.

Induction of SA to achieve better near and intermediate vision without severe degradation of distance vision is a subject of intense study. In an *in vitro* study on 3 different multifocal IOL's, the lenses induced negative SA, which were a function of pupil sizes in some designs.[14] In another simulation study, the authors stressed on greater attention to coma and SA for better outcomes with multifocal designs.[15] These multifocal designs of lenses need to be adjusted

further in patients with post-refractive surgery corneas, which had a different corneal SA compared to normal corneas.[16] For the same refractive error, coupling of different SA's led to different outcomes even with identical multifocal designs of contact lenses.[17] Further, pupil size and residual refractive error significantly impacted the performance of contact lenses.[17] Patient specific measurements showed induction of negative SA had greater benefit at near vision while positive SA had greater benefit at intermediate vision.[18] Another optical bench study showed that the lens inducing controlled levels of SA performed better at near and distance vision than a diffractive lens.[19] Hyperopic refractive surgery would result in better near, intermediate and distance outcomes, if optimal threshold of SA was known a priori.[10] In this study, there was a near homogenous distribution of number of patients between the groups in normal and diabetic eyes (Figure 2). However, an eye belonging to 1.2 to 1.6D group would be under corrected for near and intermediate vision, if the treatment was designed assuming 0 to 0.4D instead. Therefore, the mean results presented in Table 2 would be only of academic importance. Thus, patient specific measurements of threshold SA would probably be the best approach for better laser or lens based treatments of presbyopic eyes.

Using another adaptive optics simulator in younger eyes (less than 32 years of age), induction of both positive and negative spherical aberration increased the depth of focus.[8] Induction of negative SA after laser refractive surgery improved the near vision of the patients.[20] Another study also reported similar outcomes.[21] Thus, the results of this study reaffirmed the hypothesis that induction of negative SA with patient-specific testing of visual optics can provide more precise outcomes of presbyopia treatments, either with the laser or with implantable lenses. It was also suggested that visual testing in the presence of accommodation may yield enhanced

depth of focus by modulating other higher order aberrations such as coma and trefoil.[8] There is also evidence that coupling of coma and trefoil resulted in improvement of retinal image and visual quality.[22] Thus, future studies need to investigate whether targeted modulation of other higher order aberrations in addition to SA could result in further improvement in VA.

A few studies investigated the effect of diabetes on accommodative power of patient eyes. Eyes with Type 1 diabetes had lower subjective and objective accommodation amplitude than normal eyes.[4] It was also reported that age had a greater impact on the accommodation amplitude than duration of diabetes.[4] Further, the rate of change of accommodation amplitude was lower in diabetic eyes than normal eyes.[4] Another study reported a decrease in accommodation amplitude in normal and diabetic eyes with age, with the diabetic eyes having almost the same rate of the decrease as the normal eyes after adjustment for age.[23] However, a significant number of eyes had diabetic retinopathy.[23] In another study on juvenile diabetes, accommodation between the normal and diabetic eyes were similar and the diabetic eyes had minimal or no structural changes in the retina.[24] Since the biophysical properties of the human lens in type 2 diabetes were very similar to normal eyes in the older age group, the results from this study were very interesting and supported physiology.[1] Nonetheless, the biophysical properties (e.g. refractive index, hydration, lens shape) of the lens in Asian-Indian eyes requires further study since baseline VA of diabetic eyes at near and intermediate targets were better than that of normal eyes. This study clearly showed that healthy presbyopia eyes clearly benefited with targeted induction of ΔSA_T. Diabetic eyes with no clinical signs of diabetic retinopathy also behaved similarly. However, the amount of induced SA needed in diabetic eyes was much lower since the baseline VA of diabetic eyes was much better than the same of the healthy presbyopia

eyes. Repeatability of aberrometric measurements with VAO was already established in a recent study and wasn't a confounder.[12,25] This is the first study to demonstrate this effect with a novel adaptive optics visual simulator in patient eyes. This holds tremendous promise for design of patient specific treatment of presbyopia irrespective of presence or absence of disease such as diabetes. Further studies related to changes in contrast sensitivity and its' correlation to changes in VA at threshold value of negative SA need to be performed.

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Figure legends

Figure 1: Percentage distribution of eyes requiring Dioptric correction equivalent (eq. 1) to the threshold value of negative spherical aberration in normal and diabetic eyes.

Figure 2: Dot plot of induced negative spherical aberration (SA), change in visual acuity (VA) at 40 cm, 80 cm and distance in diabetic and normal eyes. Unit of y-axis in μm for SA. VA was plotted in decimal units.

Figure 1

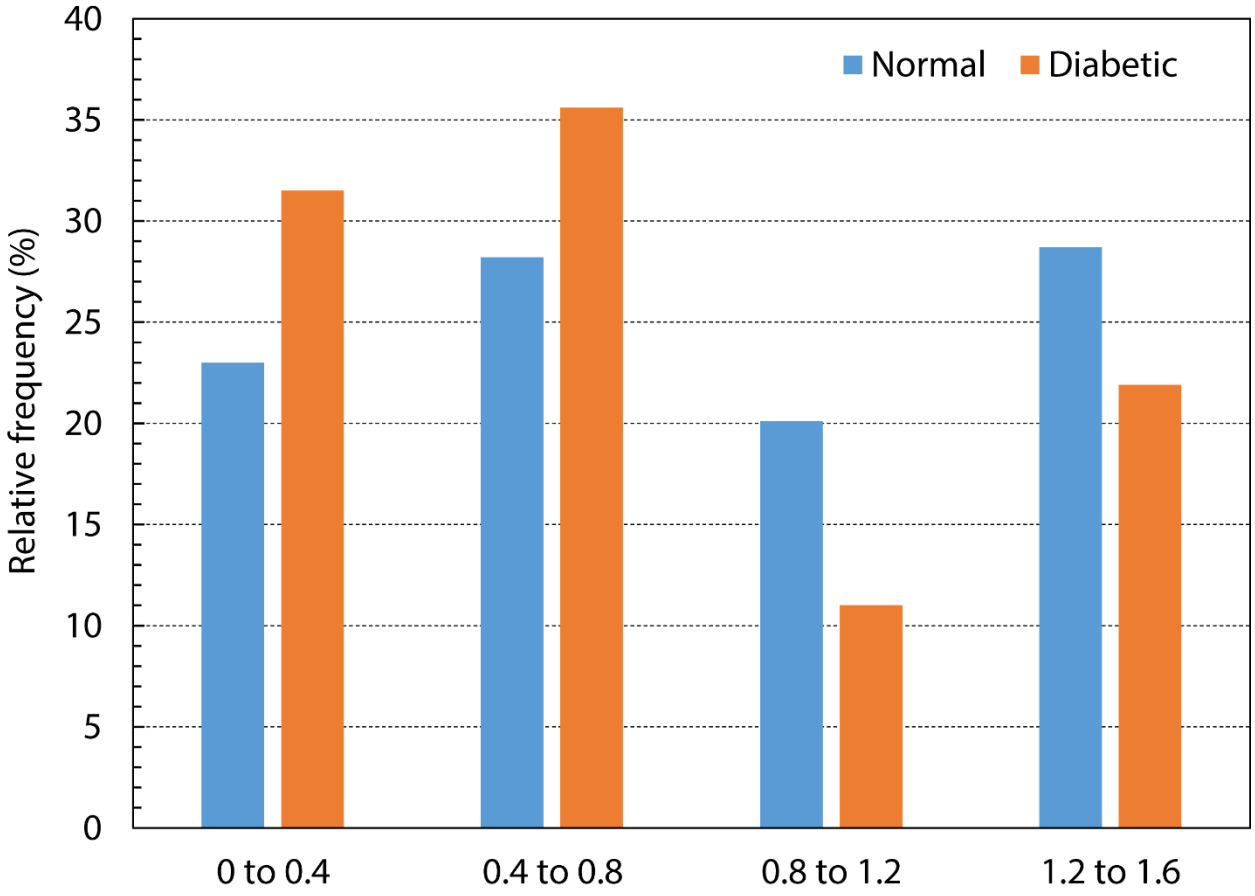

Figure 2

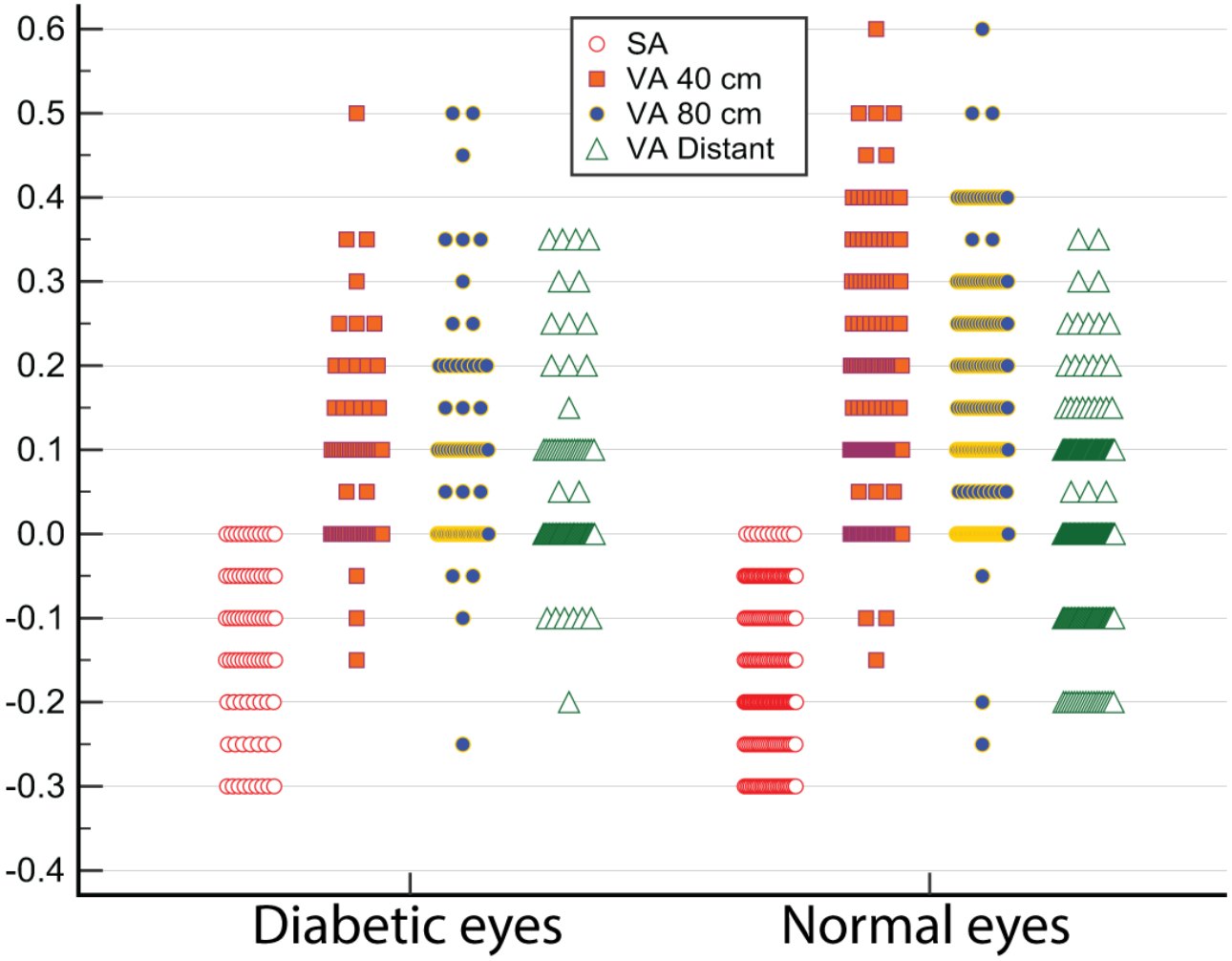

Table 1: Median of all the variables in healthy and diabetic presbyopic eyes

	Median [Min, Max]		p-value
	Normal presbyopic eyes (n=174)	Diabetic presbyopic eyes (n=73)	
Age (Years)	45 [40, 66]	47 [40, 67]	0.01*
Baseline pupil diameter (mm)	5.1 [2.7, 7.4]	5.8 [2.8, 7.4]	0.032*
Pupil diameter after ΔSA_T (µm) was induced	5.2 [2.6, 7.3]	5.7 [2.7, 7.3]	0.001*
Sphere (Diopters)	0 [-4, 2.5]	0 [-1.5, 1.5]	0.12
Cylinder (Diopters)	-0.25 [-4, 1.25]	-0.34 [-2, 0.5]	0.02*
Axis (degrees)	77.5 [0, 180]	99.5 [0, 170]	0.002*
Root mean square of higher order aberrations (µm)	0.16 [0.0,0.52]	0.18 [0,0.0.35]	0.04*

Table 2: Rows 1 to 4 show the uncorrected visual acuity and spherical aberration at baseline. Rows 5 to 9 show the change in visual acuity after adding (Δ) a negative spherical aberration. Here, uncorrected distance refractive error was corrected with the device before ocular spherical aberration was modified. Median values are shown below.

	Median [Min, Max]		p-value
	Normal presbyopic eyes (n=174)	Diabetic presbyopic eyes (n=73)	
SA (µm) [baseline]	0.03 [-0.17, 0.28]	0.02 [-0.08, 0.12]	0.44
VA at 40 cm (baseline)	0.4 [0.1, 1.25]	0.8 [0.2, 1]	0.001*
VA at 80 cm (baseline)	0.63 [0.2, 1.25]	0.8 [0.2, 1]	0.001*
VA at infinity (baseline)	0.9 [0.4, 1]	0.9 [0.4, 1]	0.87
Change in VA at 40 cm after induced ΔSA_T	0.1 [-0.15, 0.6]	0.1 [-0.15, 0.5]	0.001*
Change in VA at 80 cm after induced ΔSA_T	0.15 [-0.25, 0.6]	0.1 [-0.25, 0.5]	0.001*
Change in VA at infinity after induced ΔSA_T	0 [-0.2, 0.35]	0 [-0.2, 0.35]	0.01*
ΔSA_T (µm)	-0.15 [0, -0.3]	-0.15 [0, -0.3]	0.03*
ΔSA_T (D)	-0.8 [0, -1.59]	-0.8 [0, -1.59]	0.03*

HOA_{RMS} = Root mean square of Higher order aberration, SA = Spherical aberration, VA = Visual Acuity, ΔSA_T = Threshold value of induced SA at which maximum improvement in near and intermediate vision was obtained.