

Research Article

Use of Tear Substitutes to enhance the Image Quality of the Optic Nerve and Retina by Optical Coherence Tomography

Rai Tanvi Ravindranath¹ , Nayak Vittal Irvathur^{2,*} , Alhaj Farhath Tasneem² ,
Channabasappa Seema² , Achar Myna³ 

¹Prasad Nethralaya, Udipi, India

²Department of Ophthalmology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, India

³Lion's Sadhuram Postgraduate Institute of Ophthalmology, Hyderabad, India

Abstract

Background & Objectives: Dry eye disease (DED) has become very prevalent, with the increased usage of internet and video terminals. The present study was carried out to compare the efficacy of tear substitutes in enhancing the signal strength of measurements of optic nerve head, retinal nerve fiber layer and macula by Optical coherence tomography (OCT), and resultant change in image quality. Thus proving the role of artificial tear substitutes in increasing the diagnostic accuracy of Optical coherence tomography (OCT) measurements. **Methods:** A double blinded randomized control trial was performed on one hundred and fifty patients needing optical coherence tomography. They were randomly allocated into three groups to receive any one of the three tear substitutes Group 1 –Sodium hyaluronate (Molecular Weight M Wt 799.6g/mol) Group 2 – Poly ethylene glycol (Molecular Weight M Wt 400g/mol), Group -3 Hydroxy Propyl Methyl cellulose (Molecular Weight M Wt 1261.4 g/mol); Measurement of signal strength for optic nerve head, retinal nerve fiber thickness RNFL and sub foveal thickness SFT was done before and after instillation of tear substitutes. Data was analyzed using the Statistical Package for Social Sciences SPSS 22 version software. P value <0.05 was considered statistically significant. **Results:** The groups were comparable with respect to mean age and gender distribution. The mean signal strength (SS) of Optic Nerve Head (ONH) evaluation improved in all the groups in both eyes. The increase was the highest in Group II in both eyes. The increase in retinal nerve fiber layer thickness [RNFL] was seen in both eyes in all the groups. Improvement in macular evaluation sub foveal thickness (SFT) was seen in Group II of both eyes and group III in the Left eye. **Interpretation and Conclusion:** All tear substitutes improved the quality of the image but the improvement varied with regard to the parameters measured, thus proving artificial tear application is an essential for Optical coherence tomography OCT measurements in persons prone to dry eye This reduces the scope for error due to bad images and thereby the possibility of misdiagnosis of ophthalmic disease.

Keywords

Dry Eye Disease, Optical Coherence Tomography, Signal Strength of ONH, Sub Foveal Thickness, Retinal Nerve Fiber Layer Thickness, Sodium Hyaluronate, Polyethylene Glycol, Hydroxy Propyl Methyl Cellulose

*Corresponding author: ivittal78@gmail.com (Nayak Vittal Irvathur)

Received: 14 April 2024; **Accepted:** 26 August 2024; **Published:** 26 September 2024



Copyright: © The Author(s), 2024. Published by Science Publishing Group. This is an **Open Access** article, distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

1. Introduction

Worldwide, Dry Eye Disease (DED) is becoming a major contributor to ocular morbidity. [1] DED represents a multifactorial, heterogeneous disorder of the precorneal tear film, which results in ocular surface disease. The tear film and ocular surface form a complex and stable system that can lose its equilibrium due to numerous disturbing factors. When dry eye problems appear, a decline in quality of life is unavoidable. These symptoms vary from minor, transient irritation to persistent dryness, burning, itching, redness, discomfort, ocular fatigue, and visual disruption. [2] Dry eye affects between 5% and 34% of individuals worldwide; prevalence rises sharply with advancing age. The prevalence of DED is significantly impacted by geographic location, climatic circumstances, and people's lifestyles. As per a recent study from north India, the prevalence of dry eye disease (DED) was estimated to be 32%, with 81 percent of cases being classified as severe Dry Eye Disease (DED) based on symptoms. [3] Dry Eye Disease (DED) incidence was observed to be 1.46 percent in another study from south India. [4] About 10% of dry eye patients have a condition that is only aqueous-deficient. More than 80% of cases are caused by mixed hyper evaporative/aqueous-deficient forms, which are typically brought on by meibomian gland dysfunction. [5] Functional vision is compromised by dry eyes, particularly when reading, using a computer, or driving. The severity of the condition is correlated with a significant reduction in reading speed. [6]

Optical coherence tomography (OCT) is used to create high-resolution images of ocular components. It employs laser light to produce two-dimensional images that show the retina's layers or optic nerve. Glaucoma, optic nerve disease, macular edema diabetic or cystoid, macular holes are a few diseases that are detected and assessed using optical coherence tomography. [7] During an OCT scan, the patient is required to stare at a target on a video display for several minutes, and at various points, they are told to keep the eye being scanned open while the images are being taken. The corneal tear film plays a crucial role in maintaining a uniform, smooth optical surface. [8, 9] Previous research has demonstrated that focusing intensively on an object, such as a book or a video display device, causes the blink rate to decrease and the rate of tear evaporation to increase. [10, 11]

Therefore, it is likely that greater tear evaporation occurs during OCT scanning sessions as a result of extended looking and avoidance of blinking.

The likelihood of receiving lower-quality images increases with the length of OCT scanning sessions. Additionally, it was shown that the scan quality clearly increases when the patient is told to blink. Measurements in optical coherence tomography, a light-based imaging technique, depend on the light source's capacity to enter and exit the eye. While the somewhat rough surface of the eye with a damaged tear film could scatter the measuring beam and impair image quality, a

smooth optical surface maintained by the tear film would allow for minimum scattering of the light and subsequently reflected light. [7] The corneal tear film plays a crucial role in maintaining a uniform, smooth optical surface. [8, 9]

2. Aim and Objectives of the Study

1) To compare the efficacy of tear substitutes in enhancing the signal strength for Optic Nerve Head ONH measurement before and after the instillation of three tear substitutes 2) To measure the signal strength of optic nerve head (ONH) parameters, retinal nerve fibre layer RNFL thickness, and subfoveal thickness SFT before and after the instillation of three tear substitutes Group 1 – Sodium hyaluronate (Molecular Weight M Wt 799.6g/mol) Group 2 – Poly ethylene glycol (Molecular Weight M Wt 400g/mol), Group -3 Hydroxy Propyl Methyl cellulose (Molecular Weight M Wt – 1261.4 g/mol);

3. Materials and Method

3.1. Source of Data and Study Population

Patients who attended the ophthalmology outpatient department for eye evaluation at Vydehi Institute of Medical Sciences and Research Centre, Whitefield Bengaluru after getting informed consent. (briefly explaining to the patient in the language that he/she understands regarding the tests that he/she has to undergo).

It was a randomized controlled trial between January 2021 to June 2023 with a sample size of one hundred and fifty (150) patients. The sample size was calculated assuming the expected mean and standard deviation of the radius of curvature after the instillation of artificial tears in the eyes. Group 1 Sodium hyaluronate as, σ 0(800.72,441.24), in the Group 2 Polyethylene glycol as, σ 0(473.36,160), and in the Group 3 Hydroxy propyl methyl cellulose as, σ 0 (574.06,171.42), as per the previous study by Ghazi et al. The other parameters considered for sample size calculation included were 80% power of the study and 5% two-sided alpha error. The required sample size was calculated using ANOVA: F tests - ANOVA: Fixed effects, omnibus, one-way Analysis: A priori: Compute the required sample size Input: Effect size $f = 0.2583$ α err prob = 0.05 Power $(1 - \beta$ err prob) = 0.80 Number of groups =3 Output: Non centrality parameter $\lambda = 10.0082$ Critical F = 3.0576 Numerator df = 2 Denominator df = 147 Total sample size = 150 Actual power = 0.8073 The required sample size as per the above-mentioned calculation was 50 in each group. Hence the final required sample size would be 150.

Inclusion Criteria: Patients included in this study were those requiring Optical coherence tomography OCT evalua-

tion of the optic nerve head, peri papillary retina and macula. Exclusion criteria: Patients having central lenticular opacity, central corneal opacity, nystagmus, optic atrophy, Myopia >4D, Astigmatism >3D, Hypermetropia >4D.

3.2. Method of Collection of Data

This study was conducted as a randomized control trial study, wherein written informed consent was taken prior to the investigation after detailed information was given to the participants regarding the study. 150 patients selected were randomly allocated into 3 groups (50 in each group) by lottery method. All the patients underwent refractive testing, Schirmer’s tests 1 & 2, baseline measurement of signal strength of OCT image, measurement of retinal nerve fiber thickness RNFL, and central sub foveal thickness SFT. Allocation concealment was done by the serially numbered opaque sealed envelope (SNOSE) method. Each group was instilled one particular tear substitute of known viscosity and molecular weight, following which signal strength of OCT ONH image, OCT measurement of retinal nerve fiber layer RNFL thickness, and central sub foveal thickness were recorded again.

The study participants, the person who was going to instill the eye drop, and the investigator who was going to measure the outcome variable, were blinded to reduce bias. Tear substitutes used for each group are

Group 1- Sodium hyaluronate (molecular weight 799.6g/mol)

Group 2- Polyethylene glycol (molecular weight 400 g/mol)

Group 3- Hydroxy propyl methyl cellulose (molecular weight 1261.4g/mol)

Materials used:

Tear substitutes as per molecular weight, Viscosity Cirrus 4000 Model spectral domain optical coherence tomography machine Snellen chart, Jaeger’s near-vision chart, Ishihara color vision chart chirmer’s test strips.

3.3. Statistical Methods

Right eye (RE) ONH SS Signal Strength, Left eye (LE) ONH SS Signal Strength, RE RNFL Thickness, LE RNFL Thickness, RE SFT sub foveal thickness, and LE SFT sub foveal thickness were considered as the outcome variables. The study group (Group 1, Group 2, and Group 3) was considered the primary variable.

Age, gender, were considered study-relevant variables.

Data was also represented using appropriate diagrams like Error bar charts, Cluster bar charts, and box plots.

For normally distributed Quantitative parameters the mean values were compared between study groups using ANOVA (more than 2 groups). For non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Kruskal Wallis Test (P Value) (>2 groups).

Categorical outcomes were compared between study groups using the Chi-square test. P value < 0.05 was considered statistically significant. Data was analyzed by using Statistical package for Social Sciences SPSS 22 version software. [12]

4. Results

A total of subjects 150 subjects were included in the final analysis. The mean Age with in Group 1 was 47.06 ± 11.44 , it was 47.76 ± 12.31 Group 2 and it was 45.14 ± 13.07 in Group 3. The mean difference of Age in Study Group was statistically not significant with P value 0.5452 while comparing Gender with Study Group in the study population. In Group 1, 35 (70.00%) participants were male and 15 (30.00%) were female. In Group 2, 34 (68.00%) were male and 16 (32.00%) were female. In Group 3, 36 (72.00%) were male and 14 (28.00%) were female. The difference in the proportion of gender between the study group was statistically not significant with P-value 0.9092. Comparison of the RE (ONH SS Before) and RE (ONH SS After)

Table 1. RE (ONH SS Before).

Parameter	Study Group (Median (IQR))	Kruskal Wallis Test (P Value)
Group 1 (N=50)Group 2 (N=50)Group 3 (N=50)RE (SS Before)		
4.50(4.0 to 5.0)	5.00(4.0 to 5.0)	5.00(4.25 to 5.75) 0.0188

The median RE (SS Before) with in Group 1 was 4.50(4.0 to 5.0), it was 5.00(4.0 to 5.0) in Group 2 and it was 5.00(4.25 to 5.75) in Group 3. The median difference of RE (SS Before) in Study Group was statistically significant with P value 0.0188.

Table 2. RE (ONH SS After).

Parameter	Study Group (Median (IQR))	Kruskal Wallis Test (P Value)
Group 1 (N=50)Group 2 (N=50)Group 3 (N=50)RE (SS After)		
5.00(5.0 to 6.0)	6.00(6.0 to 6.75)	6.00(5.0 to 6.0) 0.0021

The median RE (SS After) with in Group 1 was 5.00(5.0 to 6.0), it was 6.00(6.0 to 6.75) in Group 2 and it was 6.00(5.0 to 6.0) in Group 3. The median difference of RE (SS After) in Study Group was statistically significant with P value 0.0021.

Comparison of LE (ONH SS Before) and LE (ONH SS After)

Table 3. LE (ONH SS Before).

Parameter	Study Group (Median (IQR))	Kruskal Wallis Test (P Value)
Group 1 (N=50)Group 2 (N=50)Group 3 (N=50)LE (SS Before)		
5.00(5.0 to 5.0)	5.00(5.0 to 6.0)	5.00(5.0 to 6.0) 0.0551

The median LE (ONH SS Before) with in Group 1 was 5.00(5.0 to 5.0), it was 5.00(5.0 to 6.0) in Group 2 and it was 5.00(5.0 to 6.0) in Group 3. The median difference of LE (ONH SS Before) in Study Group was statistically not significant with P value 0.0551.

Table 4. LE (ONH SS After).

Parameter	Study Group (Median (IQR))	Kruskal Wallis Test (P Value)
Group 1 (N=50)Group 2 (N=50)Group 3 (N=50)LE (SS After)		
6.00(5.0 to 6.0)	7.00(6.0 to 7.0)	6.00(5.0 to 6.0) <0.001

The median LE (ONH SS After) with in Group 1 was 6.00 (5.0 to 6.0), it was 7.00 (6.0 to 7.0) in Group 2 and it was 6.00(5.0 to 6.0) in Group 3. The median difference of LE (ONH SS After) in Study Group was statistically significant with P value <0.001.

Comparison of RE (RNFL Thickness Before and After)

Table 5. RE (RNFL Thickness Before).

Parameter	Study Group (Median (IQR))	Kruskal Wallis Test (P Value)
Group 1 (N=50)Group 2 (N=50)Group 3 (N=50)RE (RNFL Thickness Before)		
72.00 (69.0 to 78.0)	74.00 (68.25 to 78.0)	76.50 (72.0 to 82.0) 0.0335

The median RE (RNFL Thickness Before) with in Group 1 was 72.00(69.0 to 78.0), it was 74.00(68.25 to 78.0) in Group 2 and it was 76.50(72.0 to 82.0) in Group 3. The median difference of RE (RNFL Thickness Before) in Study Group was statistically significant with P value 0.0335.

Table 6. RE (RNFL Thickness After).

Parameter	Study Group (Median (IQR))			Kruskal Wallis Test (P Value)
Group 1 (N=50) Group 2 (N=50) Group 3 (N=50) RE (RNFL Thickness After)				
	72.50(69.25 to 79.0)	75.00(70.0 to 79.0)	77.50(72.0 to 83.0)	0.0356

The median RE (RNFL Thickness After) with in Group 1 was 72.50(69.25 to 79.0), it was 75.00(70.0 to 79.0) in Group 2 and it was 77.50(72.0 to 83.0) in Group 3. The median difference of RE (RNFL Thickness After) in Study Group was statistically significant with P value 0.0356.

Comparison of LE (RNFL Thickness Before and After)

Table 7. LE (RNFL Thickness Before).

Parameter	Study Group (Median (IQR))			Kruskal Wallis Test (P Value)
Group 1 (N=50) Group 2 (N=50) Group 3 (N=50) LE (RNFL Thickness Before)				
	72.00(69.0 to 76.0)	73.50(69.0 to 77.75)	76.00(73.0 to 82.0)	0.0014

The median LE (RNFL Thickness Before) with in Group 1 was 72.00(69.0 to 76.0), it was 73.50(69.0 to 77.75) in Group 2 and it was 76.00(73.0 to 82.0) in Group 3. The median difference of LE (RNFL Thickness Before) in Study Group was statistically significant with P value 0.0014.

Table 8. LE (RNFL Thickness After).

Parameter	Study Group (Median (IQR))			Kruskal Wallis Test (P Value)
Group 1 (N=50) Group 2 (N=50) Group 3 (N=50) LE (RNFL Thickness After)				
	72.50(69.25 to 76.0)	74.50(70.0 to 78.75)	76.00(74.0 to 83.0)	0.0022

The median LE (RNFL Thickness After) with in Group 1 was 72.50(69.25 to 76.0), it was 74.50(70.0 to 78.75) in Group 2 and it was 76.00(74.0 to 83.0) in Group 3. The median difference of LE (RNFL Thickness After) in Study Group was statistically significant with P value 0.0022.

Comparison of RE (SFT Before and After)

Table 9. RE (SFT Before).

Parameter	Study Group (Median (IQR))			Kruskal Wallis Test (P Value)
Group 1 (N=50) Group 2 (N=50) Group 3 (N=50) RE (SFT Before)				
	238.00(230.25 to 245.0)	234.50(224.0 to 245.0)	238.00(228.0 to 243.5)	0.5176

The median RE (SFT Before) with in Group 1 was 238.00(230.25 to 245.0), it was 234.50(224.0 to 245.0) in Group 2 and it was 238.00(228.0 to 243.5) in Group 3. The median difference of RE (SFT Before) in Study Group was statistically not significant with P value 0.5176.

Table 10. RE (SFT After).

Parameter	Study Group (Median (IQR))	Kruskal Wallis Test (P Value)
Group 1 (N=50)Group 2 (N=50)Group 3 (N=50)RE (SFT After)		
238.00(231.0 to 246.0)	235.50(224.25 to 246.0)	238.00(228.0 to 243.75) 0.5827

The median RE (SFT After) with in Group 1 was 238.00(231.0 to 246.0), it was 235.50(224.25 to 246.0) in Group 2 and it was 238.00(228.0 to 243.75) in Group 3. The median difference of RE (SFT After) in Study Group was statistically not significant with P value 0.5827.

Comparison of LE (SFT Before and After)

Table 11. LE (SFT Before).

Parameter	Study Group (Median (IQR))	Kruskal Wallis Test (P Value)
Group 1 (N=50)Group 2 (N=50)Group 3 (N=50)LE (SFT Before)		
236.00 (230.25 to 245.0)	237.00 (225.5 to 246.75)	235.50 (228.5 to 244.75) 0.8718

The median LE (SFT Before) with in Group 1 was 236.00(230.25 to 245.0), it was 237.00(225.5 to 246.75) in Group 2 and it was 235.50(228.5 to 244.75) in Group 3. The median difference of LE (SFT Before) in Study Group was statistically not significant with P value 0.8718.

Table 12. LE (SFT After).

Parameter	Study Group (Median (IQR))	Kruskal Wallis Test (P Value)
Group 1 (N=50)Group 2 (N=50)Group 3 (N=50)LE (SFT After)		
236.00(230.5 to 246.0)	237.50(225.5 to 246.75)	236.00(229.25 to 245.5) 0.8879

The median LE (SFT After) with in Group 1 was 236.00(230.5 to 246.0), it was 237.50(225.5 to 246.75) in Group 2 and it was 236.00(229.25 to 245.5) in Group 3. The median difference of LE (SFT After) in Study Group was statistically not significant with P value 0.8879.

5. Discussion

Dry eye disease (DED) is one of the major contributors to ocular morbidity. [1] There is a decline in the quality of life with dry eye syndrome. Increased use of video display devices has led to dry eyes becoming more common in the general public. Optical coherence tomography OCT is one of the commonly performed test to document the anterior and posterior segment structures of the eye. Optical coherence tomography OCT is used to create high-resolution images of ocular components. It has been extensively used in glaucoma-affected, diabetic eyes for assessing the changes in the

optic nerve, retinal nerve fiber layer thickness and sub foveal thickness. Hence the present study was carried out to compare the efficacy of three tear substitutes in enhancing the signal strength in Optical coherence tomography OCT data and the change in image quality.

The objectives of the present study were comparable with that of the studies by Wozniak PA et al. [13] Hannemann E et al. [14] Carracedo G et al. [15] Napoli PE et al. and [16] Wozniak PA et al. [13] who compared the effect of different lubricant eye gels on tear film thickness. Hannemann E et al. [14] in their study compared hyaluronic acid-containing tear substitutes of different viscosities. Carracedo G et al. [15] in their study compared different concentrations of sodium hyaluronate ophthalmic solutions. Napoli PE et al. [16] in their study evaluated dynamic changes induced by three different artificial tears in the pre corneal tear film and lower tear meniscus using spectral domain anterior segment OCT. The present study compared the following three tear substitutes -

Sodium hyaluronate, Polyethylene glycol, and Hydroxy propyl methyl cellulose as a randomized controlled trial with the blinding of both the study participants and the investigator. A total of 150 subjects requiring optical coherence tomography OCT evaluation of the optic nerve head and the macula, attending the ophthalmology OPD of a tertiary care center were the subjects of this study.

Hyaluronate is a strongly hydrophilic, naturally occurring, non sulfated glycosaminoglycan. Wozniak PA et al. [13] did a single masked observer-blinded randomized study on a total of 60 subjects with DED by dividing into 3 groups and received Hyaluronic acid 0.2% (HA) or Polyethylene Glycol 0.4% - Propylene Glycol 0.3% (PG-PRG) or Trehalose 3%-Hyaluronic Acid 0.15% (TH-HA). Napoli PE et al. [16] in their study prospectively examined 42 normal human eyes for changes in pre corneal tear film and lower tear meniscus. They obtained all tear film images before and after the installation of three different types of artificial tears (muco mimetic, lipid-based, and saline) in five serial scans. Subjects received a drop of 35 microlitres in one randomly selected eye. Hannemann E et al. [14] investigated in 20 healthy volunteer subjects, the influence of hyaluronic acid-containing tear substitutes of different viscosities on the measurement results of OCT and on the non-invasive tear film break-up time.

The three hyaluronic acid tear substitutes of different viscosities "Hylo-Vision 0.1%, 0.2%, 0.3%, OmniVision GmbH, Puchheim, Germany" were measured using OCT-2000 (Topcon, Hamburg, Germany) and kinematograph.

Carracedo G et al [15] in their experimental, double-masked, randomized study included 23 healthy subjects. They instilled 35 µl of 0.1%, 0.2%, and 0.3% Sodium Hyaluronate ophthalmic solutions and saline solution in a randomly assigned eye and observed measurements of tear meniscus measurements like height, depth, and turbidity using OCT at various time intervals.

The present study included a total of 150 subjects with 50 subjects in each group. There was no statistically significant difference between the groups with respect to mean age and gender. Wozniak PA et al. [13] also noted no significant difference between the groups with respect to mean age and gender. Hannemann E et al. [14] observed a median age of only 28.5 years as their study was done in only healthy volunteers.

Carracedo G et al. [15] in their study observed the mean age was only 23.57 ± 2.56 years as they also included only healthy subjects attending the optometry clinic of the faculty of optic and optometry at the university of Madrid. The prevalence of dry eyes is expected to increase with the increase in age. The mean age was comparable between the three groups in the present study. The mean age was highest in Group 2 (Polyethylene glycol) at 47.76 years and was lowest in Group 3 (Hydroxy propyl methyl cellulose) at 45.14 years. Adults aged above 40 years can have a prevalence as high as 75%, with women being most commonly affected. The mean age of the subjects in the present study was also more than

40 years in all the groups.

Wozniak PA et al. [13] in their study observed the mean age was 45.6 ± 13.4 years. The etiology varies from person to person. Reduced tear production, increased tear evaporation, and abnormalities in the formation of mucus or lipids in the tear film are all contributing factors to dry eye disease. Out of the 150 subjects totally in the present study, 70% (105) were males. The gender distribution was comparable between the three groups. In each group, the proportion of males was significantly higher than females. This could be due to the presentation of males easily to the outpatient department and their easy access to ophthalmic care as compared to females. The proportion of females was higher ($37/60=62\%$) in the study by Wozniak PA et al. [13], as also Carracedo G et al. [15] (16 women and seven men), and Hannemann E et al. [14] (11 women and 9 men).

Optic Nerve Head Signal Strength (SS)

In Right eye: The median SS ONH (after instillation) improved in all the groups. It improved to 5 in group 1 and to 6 in Groups 2 and 3. The increase was highest in Group 2 (Polyethylene glycol) with median SS ONH increasing from the inter quartile range IQR of (4 to 5) before instillation to (6 to 6.75) after instillation. There was also a statistically significant difference across the groups with regard to SS ONH after the instillation of tear substitutes.

In Left eye: The median SS ONH (after instillation) improved in all the groups. There was also a statistically significant difference across the groups.

The increase was highest in Group 2 (Polyethylene glycol) with median SS ONH increasing from the inter quartile range IQR of (5 to 6) before instillation to (6 to 7) after instillation. In the present study, signal strength improved in all the groups in both eyes. But the maximum improvement was seen in the polyethylene glycol group, Group 2.

Retinal Nerve Fiber layer (RNFL) thickness:

In Right eye: The difference in median RNFL thickness (before instillation) across the groups was statistically significant. It was lower in Group 1 at 72 µm compared to the other groups (median RNFL thickness in group 2 = 74 µm and 3 = 76.5 µm).

The improvement in median RNFL thickness (after instillation) was seen in all the groups. It improved to 72.5 µm in group 1 and to 75 µm in Group 2 and 77.5 µm in Group 3. The increase was highest in Group 2 (Polyethylene glycol) and Group 3 (Hydroxy propyl methyl cellulose) after instillation. There was also a statistically significant difference across the groups with regard to RNFL thickness after the instillation of tear substitutes.

In Left eye: The difference in median RNFL thickness (before instillation) across the groups was statistically significant. It was lower in Group 1 at 72 µm compared to the other groups (median RNFL thickness in group 2 = 73.5 µm and 3 = 76 µm).

The improvement in median RNFL thickness (after instillation) was seen in groups 1, 2, and 3 It improved to 72.5 µm

in group 1 and 74.5 μm in Group 2 and 76 μm in Group 3. The increase was highest in Group 2 (Polyethylene glycol) after instillation. There was also a statistically significant difference across the groups with regard to RNFL thickness after the instillation of tear substitutes.

Subfoveal Thickness (SFT):

In Right eye: The difference in median SFT (before instillation) across the groups was statistically not significant. It was comparable between the groups with the lowest in Group 2 at 234.5 μm compared to the other groups (median thickness in group 1 and 3 = 238 μm).

The improvement in median SFT (after instillation) was seen only in Group 2 from 234.5 to 235.5 μm . There was no increase in median SFT after instillation in groups 1 and 3. There was no statistically significant difference across the groups with regard to SFT after the instillation of tear substitutes.

In Left eye: The difference in median SFT (before instillation) across the groups was statistically not significant. It was comparable between the groups with the lowest at in Group 3 at 235.5 μm compared to the other groups (median thickness in group 2 = 237 μm).

The improvement in median SFT (after instillation) was seen only in Groups 2 and 3. There was no statistically significant difference across the groups with regard to SFT after the instillation of tear substitutes.

Wozniak PA et al. [13] in their study observed that ten minutes after instillation, a pronounced increase in Tear Function Tests was observed in all groups. The combination of Trehalose 3% + Hyaluronic acid 0.15% offered a significantly longer increase in Tear Function tests indicating a longer retention time.

Hannemann E et al. [14] in their study observed that non-invasive tear film break-up time improved significantly ($p = 0.027$) after the application of 0.3% hyaluronic acid. There was no significant difference in all OCT parameters used before and after the application of the different viscous hyaluronic acid-containing tear substitutes. They concluded there was no influence of tear substitutes containing different viscosities of hyaluronic acid on the measurement results of optical coherence tomography. Napoli PE et al. [16] in their study observed that spectral-domain OCT imaging has preliminarily proved to be a noninvasive tool to evaluate, in real-time, the different changes induced by instillation of artificial tears. Carracedo G et al. [15] in their study observed that sodium hyaluronate ophthalmic solutions increase residence time in healthy subjects and are positively correlated with its concentration and therefore the viscosity.

6. Conclusion

Optical Coherence Tomography (OCT) is a non-invasive, quick, and repeatable examination that has transformed the imaging of posterior segment lesions. Optical Coherence Tomography (OCT) has been used to produce high-quality

images in the evaluation of various diseases, optic nerve head ONH in glaucoma; retinal nerve fiber layer RNFL thickness in optic nerve disease, glaucoma; Subfoveal thickness SFT in diabetic maculopathy. It is challenging to see the physiology of the eye in an OCT image with low signal strength. This makes accurate diagnosis difficult. Errors in diagnosis can have disastrous consequences. Tear substitutes used in the study were: Group 1- Sodium hyaluronate (molecular weight 799.6g/mol), Group 2- Polyethylene glycol (molecular weight 400 g/mol), Group 3- Hydroxy propyl methyl cellulose (molecular weight 1261.4g/mol)

This study compared the three tear substitutes in enhancing the signal strength SS in OCT ONH optic nerve head data and the change in image quality and thickness of Retinal nerve fiber layer RNFL, subfoveal thickness SFT. The present study was a randomized controlled trial with the blinding of both the study participants and the investigator. A total of 150 subjects requiring OCT evaluation of the optic nerve head and OCT evaluation of the macula, attending the ophthalmology outpatient department of a tertiary care center were included. They were divided into 3 groups of 50 each. There was no statistically significant difference between the groups with respect to mean age and gender. The mean age was highest in Group 2 (Polyethylene glycol) at 47.76 years and was lowest in Group 3 (Hydroxy propyl methyl cellulose) at 45.14 years.

The difference in median Signal Strength (SS) for ONH (before instillation) across the groups was statistically significant in the right eye. The median Signal Strength for ONH (after instillation) improved in all the groups in the right eye. It improved to 5 in group 1 and to 6 in Groups 2 and 3. The increase was highest in Group 2 with median SS increasing from the interquartile range IQR of (4 to 5) before instillation to (6 to 6.75) after instillation. There was also a statistically significant difference across the groups with regard to SS after the instillation of tear substitutes in the right eye.

The median SS for ONH (before instillation) across the groups was not statistically significant in the left eye. The median SS for ONH (after instillation) improved in all the groups in the left eye. There was also a statistically significant difference across the groups. The increase was highest in Group 2 with median SS increasing from the interquartile range of (5 to 6) before instillation to (6 to 7) after instillation.

The difference in median Retinal Nerve Fiber Layer (RNFL) thickness (before instillation) across the groups was statistically significant in both eyes. There was also a statistically significant difference across the groups with regard to RNFL thickness after the instillation of tear substitutes in both eyes. The improvement in median RNFL thickness (after instillation) was seen in all the groups in both eyes. The increase was highest in Group 2 and Group 3 after instillation in the right eye and highest only in Group 2 in the left eye.

The difference in median Sub-Foveal Thickness (SFT)

(before instillation) across the groups was statistically not significant in both eyes. There was no increase in median SFT after instillation in groups 1 and 3 in the right eye. The improvement in median SFT (after instillation) was seen only in Groups 2 and 3 in the left eye.

It would be expected that improvement will be more with HPMC (Hydroxy propyl methyl cellulose), which has a molecular weight of 1261 g/mol, and with sodium hyaluronate, which has a molecular weight of 799.6 g/mol. But the group with the instillation of polyethylene glycol had the highest improvement among all. This could be due to the surface tension in these eyes. The radius of the tear meniscus is a useful measure of tear volume and is likely to have implications for dry eye diagnosis. High Molecular Weight Hyaluronic acid solutions with the lowest poly dispersion index show the best shear-thinning behaviors. [17] These solutions can result in the optimal formulation for providing the longest duration of relief and the best comfort for the patient. Many factors such as constituent rheological polymer nature and concentration, specific demulcents and emollients, thickeners, gelling agents, pH, osmolarity, temperature, electrolyte concentrations, oxygen permeability, and clarity could also affect the performance of artificial tears. Natural tears are non-newtonian fluids. [18] Their viscosity depends on the shear rate. An ideal tear substitute should exhibit higher tear viscosity when the eye is opened, to prevent the break of tear film and drainage. An ideal tear substitute should also exhibit reduced viscosity during blinking to prevent epithelial surface damage. The present study compared the efficacy of three tear substitutes in enhancing the signal strength of optic nerve head, Retinal Nerve Fiber Layer thickness, and sub foveal thickness on OCT scanning. The most probable reason was that the polyethylene & polypropylene glycol (group 2) had multifunctional action, due to presence of osmo protectants and electrolytes.

The ophthalmic practitioner, asked as to which is the best tear substitute has to first identify the cause, then decide the tear substitute. Most patients are forced to adopt a trial and error approach to product selection incurring increased cost and frustration in the process. [19]

Important considerations include formulation, concentration, molecular weight, preservative used and storage bottle design.

Aqueous based tears, containing viscosity enhancing agents –dextran, carboxy methyl cellulose, hyaluronic acid, sodium hyaluronate and products which increase tear retention time, hydroxy propyl guar, hydroxyl methyl cellulose, polyethylene glycol, used in combination are most effective in reducing the symptoms and signs of dry eye disease. Combination formulations are more effective than artificial tears with single active ingredient (19). Artificial tears containing polyethylene glycol / polypropylene glycol and carboxy methyl cellulose/ hydroxyl propyl methyl cellulose are more effective than those containing carboxy methyl cellulose/ polyethylene glycol alone. (19) Electrolytes, such as

boric acid, can act as buffering agents to stabilize the pH of formulations. [20] Benzalkonium chloride a commonly used preservative is known to be pro inflammatory and has been replaced by sodium perborate or Purite (preservative substitute based on chlorine dioxide). The artificial tears containing preservative substitutes such as rapidly disintegrating preservative sodium perborate, or Purite, are best treatment choices for Dry Eye Disease. [21, 22]

The present study has evaluated three artificial tear substitutes and their effect on signal strength SS of Optic nerve head ONH, image quality and thickness of Retinal nerve fiber layer RNFL and sub foveal thickness SFT. All tear substitutes improved the signal strength, image quality but the improvement in the three groups varied with regard to parameters measured, maximum improvement was noted in group 2, polyethylene glycol group.

Abbreviations

DED	Dry Eye Disease
OCT	Optical Coherence Tomography
HA	Sodium Hyaluronate
PEG-PRG	Polyethylene Glycol - Polypropylene Glycol
HPMC	Hydroxy propyl Methyl Cellulose
M Wt	Molecular Weight
G/mol	Gram /mole
SPSS	Statistical Package for Social Sciences
SS	Signal Strength
ONH	Optic Nerve Head
RNFL	Retinal Nerve Fiber Layer
SFT	Sub Foveal Thickness
RE	Right Eye
LE	Left Eye
ANOVA	Analysis of Variance
IQR	Inter Quartile Ratio
P value	Probability Value
TFT	Tear Function Tests
SNOSE	Serially Numbered Opaque Sealed Envelope
TH HA	Trehalose-Hyaluronic Acid

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Chatterjee S, Agrawal D, Sanowar G, Kandoi R. Prevalence of symptoms of dry eye disease in an urban Indian population. *Indian J Ophthalmol.* 2021; 69(5): 1061-6.
- [2] Lee AJ, Lee J, Saw SM, Gazzard G, Koh D, Widjaja D, et al. Prevalence and risk factors associated with dry eye symptoms: A population based study in Indonesia. *Br J Ophthalmol.* 2002; 86(12): 1347-51.

- [3] Titiyal JS, Falera RC, Kaur M, Sharma V, Sharma N. Prevalence and risk factors of dry eye disease in North India: Ocular surface disease index-based cross-sectional hospital study. *Indian J Ophthalmol*. 2018; 66(2): 207-11.
- [4] Donthineni PR, Kammari P, Shanbhag SS, Singh V, Das AV, Basu S. Incidence, demographics, types and risk factors of dry eye disease in India: Electronic medical records driven big data analytics report I. *Ocul Surf*. 2019; 17(2): 250-6.
- [5] Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea*. 2012; 31(5): 472-8.
- [6] Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. *Dtsch Arztebl Int*. 2015; 112(5): 71-81; quiz 82.
- [7] Stein DM, Wollstein G, Ishikawa H, Hertzmark E, Noecker RJ, Schuman JS. Effect of corneal drying on optical coherence tomography. *Ophthalmology*. 2006; 113(6): 985-91.
- [8] Dursun D, Monroy D, Knighton R, Tervo T, Vesaluoma M, Carraway K, et al. The effects of experimental tear film removal on corneal surface regularity and barrier function. *Ophthalmology*. 2000; 107(9): 1754-60.
- [9] Rolando M, Zierhut M. The ocular surface and tear film and their dysfunction in dry eye disease. *Surv Ophthalmol*. 2001; 45 Suppl 2: S203-10.
- [10] Schlote T, Kadner G, Freudenthaler N. Marked reduction and distinct patterns of eye blinking in patients with moderately dry eyes during video display terminal use. *Graefes Arch Clin Exp Ophthalmol*. 2004; 242(4): 306-12.
- [11] Tsubota K, Nakamori K. Dry eyes and video display terminals. *N Engl J Med*. 1993; 328(8): 584.
- [12] Statistical Package for Social Sciences SPSS 22 Version Software, Version 1.0.3. Bangalore, India.
- [13] Wozniak PA, Schmidl D, Bata AM, Fondi K, Witkowska KJ, Aranha dos Santos V, et al. Effect of different lubricant eye gels on tear film thickness as measured with ultrahigh-resolution optical coherence tomography. *Acta Ophthalmol*. 2017; 95(4): e307-13.
- [14] Hannemann E, Erb C., The Impact of Artificial Tear Viscosity on the Results of Optical Coherence Tomography. *Klin Monbl Augenheilkd*. 2021; 238(9): 1004-9.
- [15] Carracedo G, Pastrana C, Serramito M, Rodriguez-Pomar C. Evaluation of tear meniscus by optical coherence tomography after different sodium hyaluronate eyedrops instillation. *Acta Ophthalmol*. 2019; 97(2): e162-9.
- [16] Napoli PE, Satta GM, Coronella F, Fossarello M. Spectral-domain optical coherence tomography study on dynamic changes of human tears after instillation of artificial tears. *Invest Ophthalmol Vis Sci*. 2014; 55(7): 4533-40.
- [17] Arshinoff SA, Hofmann I, Nae H. Role of rheology in tears and artificial tears. *J Cataract Refract Surg*. 2021; 47(5): 655-61.
- [18] Tiffany JM, Winter N, Bliss G. Tear film stability and tear surface tension. *Curr Eye Res*. 1989; 8(5): 507-15.
- [19] Semp A David, Beeson Danielle, Sheppard Amy L, Debarun Dutta and Wolffsohn James S. Artificial Tears: A systematic review *Clin Optom (Auckl)* 2023; 15: 9-27.
- [20] MarcLabetoulle, JoseManuel Benitez –del –Castillo, Stefano Barabino, Rocio Herrero Vanrell, Phillippe Daull, Jean – Sebastian Garrigue, Maurizio Rolando Artificial tears: Biological role of their ingredients in the management of Dry Eye Disease *Int J Mol Sci* 2022 Mar; 23(5): 2434.
- [21] Baudouin C, Labbe A, Liang H, Pauly A, Brignole & Baudouin F Preservatives in eye drops, : the good, the bad, the ugly *Prog Retinal Eye Research* 2010, (29) (4) 312-334.
- [22] Kathuria A, Shamloo K, Jhanji V, Sharma A-Categorization of marketed artificial tear formulations based on their ingredients: A rational approach for their use. *J Clin Med* 2021 10(6) 1289.