Title

Influence of sodium hyaluronate concentration in tear meniscus height: 10 minutes dynamic profile after single instillation.

Running Title

Sodium hyaluronate concentration in tear meniscus height

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Table and Figures

1 Table and 4 Figures

Submission Date

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Abstract

Purpose: To assess the height, area and density of tear meniscus throughout 10 minutes after instillation of sodium hyaluronate (SH) of equal molecular weight at two different concentrations.

Methods: 34 eyes from 17 patients were enrolled is this longitudinal, non-randomized interventional and contralateral eye study. Tear meniscus height (TMH), corneal meniscus junction (CMJ), lower-lid meniscus junction (LLMJ) and tear meniscus area (TMA) images were obtained with the anterior segment module of the Deep Range Imaging Ocular Coherence Tomography [(DRI-OCT) Triton Swept-Source]. Tear meniscus density (TMD) was calculated using the image processing and analysis software by Java (ImageJ program). Sodium hyaluronate (SH) artificial tears at 0.1 % and 0.2% concentrations were instilled into all right and left eyes, respectively.

Results: Patients' mean age was 61.05 ± 11.43 years old. TMH, CMJ, LLMJ and TMA meassured at 1-, 5-, 7- and 10-minutes post-instillation of 0.1% SH proved significant differences amongst them ($p < 0.05$). SH 0.2% instillation obtained similar findings, although no significant differences were found between 1- and 3- minutes post-instillation measurements ($p > 0.05$). Fewer differences were found in TMD 0.2% SH group due to a lower baseline densitometry compared to the 0.1% group.

Conclusion: 0.2% sodium hyaluronate achieved better TMH and TMA in 1- and 3 -minutes after instillation than 0.1% concentration. However, there were no statistically significant differences between 0.1% and 0.2 % sodium hyaluronate throughout a ten-minute longitudinal profile measurement using DRI-OCT.

Keywords: tear meniscus height; tear meniscus area; sodium hyaluronate; tear film; artificial tear

Introduction

Dry eye disease is a multifactorial and common ocular surface disease[1] characterized by an ocular surface inflammation, neurosensory abnormalities, and tear film instability and hyperosmolarity. This may result in a potential decrease in visual acuity and quality, eye discomfort, and risk of ocular surface damage.[1,2] Tear film has a dynamic behavior and varies between each blink. Therefore, detecting real-time tear film change could be a more direct and objective method to evaluate dry eye.[2] Tear volume is distributed along three continuous compartments: conjunctival fornix, meniscus, and preocular film. The primary lacrimal meniscus function is to act as a fluid reservoir as it retains tear excess, produced by the blinking reflex or after eyedrop instillation.[3,4] Recently, Zheng et al.[5] proposed a new method to measure the morphology and tear meniscus (TM) clearance by anterior segment optical coherence tomography (AS-OCT).[6] TM morphology measurements such as tear meniscus height (TMH), tear meniscus depth divided into corneal meniscus junction (CMJ) and lower lid meniscus junction (LLMJ), and tear meniscus area (TMA), have a wide range of applications.[7–9] In addition, AS-OCT guarantees good measurement repeatability and allows to study changes in TM morphology after artificial tears instillation.[10,11] Jones et al.[12] used high-resolution spectral-domain optical coherence tomography (HR-SD-OCT) to report changes in the lower tear meniscus after artificial tears instillation, suggesting that the variation of tear meniscus may be easy to assess.[13] Later, Garcia-Lazaro et al.[14] demonstrated an increase in the tear meniscus volume measured with HR-SD-OCT (Copernicus HR) after instillation of two different artificial tears, with different composition and concentration, in patients with dry eye disease.

Our objective is to assess the height, area and density of tear meniscus throughout 10 minutes after instillation of SH of equal molecular weight at two different concentrations.

Methods

Study design

A longitudinal, non-randomized interventional and contralateral eye study was carried out. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Hospital Clínic de Barcelona Ethics Committee.

34 eyes from 17 patients were recruited for the study from the primary care ophthalmology consultations at hospital Clínic de Barcelona. The inclusion criteria were: (1) healthy patients, (2) over 18 years old , (3) and no dry eye disease diagnosed by break-up time (BUT), Oxford scale with slit lamp examination and ocular surface disease index (OSDI) test. All the evaluations were carried out by an expert ophthalmologist (CRL). Exclusion criteria were: (1) pregnant and lactating women, (2) eye trauma four months prior to the study, (3) nasolacrimal drainage abnormalities, (4) dry eye disease, (5) permanent or temporary occlusion of lacrimal ducts, (6) use of contact lenses, (7) known intolerance to any of the components or procedures used in the study, (8) patients who underwent cataract, glaucoma, retina or corneal surgery and (9) patients with any ocular surface severe alteration.

Subjects were tested between 4:00 PM and 7:00 PM in a small office centrally heated with a room temperature of 21.0 °C to 23.0 °C and diffuse lighting. There were no ventilation ducts over the equipment. BUT evaluation was performed after OCT measurements to avoid influencing the tear meniscus. AS-OCT images were obtained with the anterior segment module of the DRI-OCT Triton Swept-Source OCT (Topcon, Tokyo, Japan). All the images were captured using the vertical Line (Height) Anterior Segment 3.0 mm Overlap 64 scan centered in the pupil and perpendicular to lower eyelid margin. Tear meniscus height (TMH) was measured in microns using the caliper tool of the ImageNet® software. Tear meniscus area (TMA) was calculated using perimeter Heron´s formula[15] $TMA = \sqrt{p\ (p-a)\ x\ (p-b)\ x\ (p-c)}$ (Figure 1), where (p) is perimeter, (a) is the CMJ, (b) is the LLMJ and (c) is the TMH. Tear meniscus density (TMD) was calculated using the image processing and analysis software by Java (ImageJ program, National Institutes of Health, Bethesda, MD). This program performed an average pixel density in a manually selected area. The main output measurement unit was the TMD in gray scale units between 0 to 255 RGB, where 0 is a fully transparent tear and 255 is a fully opaque tear. All patients underwent a basal AS-OCT and at 1-,3-,5-,7- and 10-ten minutes after artificial tear instillation (Figure 2).

Regarding the lubricant eye drops used, a 0.1 % (1 mg/ml) SH artificial tear (Hylo-COMOD ®, Brill Pharm, Bristol Laboratories, UK) was instilled into all right eyes and a 0.2 % (2 mg/ml) SH artificial tear (Hylo-GEL®, Brill Pharma, Bristol Laboratories, UK) was instilled into all left eyes. Only a single drop (30 μL in volume) of each lubricant was applied in each eye. The scans of each eye were performed within one hour time interval so that the measurements could not be influenced by the reflex secretion of the contralateral eye. The instillation was randomized using a list of random numbers (1 for 0.1% drop and 2 for 0.2% drop) generated using SPSS statistical software. OCT image interval was control with a stopwatch. Patients were instructed to blink normally but were instructed to avoid touching their eyelids or eyes during the imaging process. Images were captured within the first second immediately after a blink. All the AS-OCT captures and measurements were performed by the same ophthalmologist (CRL).

Statistical analysis

Data was analyzed with SPSS statistics software (version 26.0 for Windows; SPSS Inc, Chicago, IL, USA). Descriptive analysis was carried out with values expressed with mean ± standard deviation (SD) and range (minimum and maximum). Data normality distribution was assessed with Shapiro-Wilk test. Differences in mean values between the two groups was assessed with U-Mann-Whitney test. Longitudinal changes along all variables in the same group were studied with Friedman test. For all tests, the level of significance was established at 95% ($P < 0.05$).

Results

Thirty-four eyes from seventeen patients were included. Mean age of the patients was 61.05 ± 11.43 (31 to 77 years old). Eleven female subjects (64.7%) and six male subjects (35.3%) enrolled this contralateral eye study. Baseline, 1-,3-,5-,7- and 10- minutes measurements and differences for TMH, CMJ, LLMJ, TMA and TMD in the 0.1% and 0.2% SH groups were presented with mean p value in Table 1. No statistically significant differences were found in any variable.

Regarding 0.1% SH longitudinal changes, TMH proved significant differences from baseline compared to all post-instillation measurements ($p < 0.05$). 1-minute post-instillation also showed significant differences compared to 3-, 5-, 7- and 10-minutes post-instillation measurements ($p < 0.05$, $p < 0.01$, $p < 0.01$ and $p < 0.01$). 3- and 5- minutes post-instillation measurements did not achieve significant differences compared to longer period measurements (7- and 10 minutes post-instillation, all, $p > 0.05$). CMJ, LLMJ and TMA showed identical results to TMH. Therefore, the maximum peak is found at the first minute after instillation and significant differences can be found in just two more minutes after instillation of SH. Finally, TMD measured by densitometry reported significant differences between the baseline measurement and 1-, 3-, 5-, 7- and 10-minutes post-instillation ($p < 0.01$, $p < 0.01$, $p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively). All comparisons of post-instillation TMD reported no significant differences amongst eachother ($p > 0.05$).

Concerning the 0.2% SH group longitudinal changes, TMH revealed significant differences from baseline compared to all post-instillation measurements ($p < 0.01$). 1-minute post-instillation also proved significant differences with 5-, 7- and 10-minutes post-instillation measurements (all, $p < 0.01$), whereas no significant differences were found between 1- and 3- minutes post-instillation measurements ($p > 0.05$). In addition, 3- and 5- minutes measurements did not achieve significant differences with all subsequent measurements (7- and 10- minutes, all, $p > 0.05$). CMJ, LLMJ and TMA attained identical findings to TMH. Therefore, the maximum peak is found between the first and third minute after instillation and seems to be more stable in the eye compared to 0.1% SH. TMD measured by densitometry reported significant differences between baseline measurement and 1- and 7- minutes post-instillation ($p < 0.01$, $p < 0.05$, respectively). Moreover, significant differences were observed between TMD 1-minute, and 3- and 5-minutes post-installation measurements ($p < 0.01$, $p < 0.05$, respectively). Fewer differences were found in the 0.2% SH group due to a lower baseline densitometry than 0.1% group. 0.1% and 0.2% SH TMH and TMA longitudinal changes were presented in a box & plot graph in Figure 3 and Figure 4, respectively.

Discussion

In this study, we have observed that there were no statistically significant differences between the height and area of tear meniscus after instillation of the same SH molecule (equal molecular weight and structure) at different concentrations (0.1% mg/ml and 0.2% mg/ml) throughout a ten-minute longitudinal profile measurement using swept source AS-OCT.

A similar study[10] obtained the same results when comparing four different types of artificial tears other than SH (different active principle, concentration, structure and molecular weight). They showed significant differences in TMH between the different types of artificial tears. However, this effect disappeared within 20 minutes after instillation. In the same line, García-Lazaro et al.[14] demonstrated a decrease in the clearance of the tear meniscus after the instillation of two different artificial tears with different concentrations. However, unlike our results, these authors performed the measurements immediately and then at 10, 30 and 60 minutes after instillation. To the best of the authors' knowledge, this study is the first assessing the behavior of tear meniscus clearance measured in TMH, CMJ, LLMJ, TMA TMD after application of the same SH molecule at two different concentrations (0.1% mg/ml and 0.2% mg/ml) using the fellow eye as comparison in healthy eyes.

Arriola-Villalobos et al.[16] were the first to show excellent repeatability and reproducibility of tear meniscus measurements obtained using Triton SS-OCT device. Zhou et al.[17] described a good between-visit and within-visit reproducibility of lower tear meniscus height (LTMH) measured with a fourier-domain ocular coherence tomography (FD-OCT). Moreover, Arriola-Villalobos found a good within-visit reproducibility of OCT LTMH measurements.[18] Similar results have been reported in the same line.[19] All these studies were based on a cross-sectional analysis, while our study was not based on studying repeatability or reproducibility, rather longitudinally studying the dynamic behavior of the tear meniscus clearance over ten minutes. Diurnal variation of the lower tear meniscus has also been reported.[20] Thus, measurements should always be taken at the same time.[21] We performed all measurements in the same time slot (between 4:00 p.m. and 7:00 p.m.) under the same conditions of ventilation and humidity.

OCT LTMH and BUT have shown good correlation, indicating that a bigger tear meniscus leads to a longer tear film BUT.[22] Actually, small OCT LTMH values have been related to a higher risk of developing severe corneal epithelial damage in dry eye patients.[23] Curiously, in this study, we observed that a higher concentration of the same SH molecule (0.2% vs. 0.1%), produces higher temporal values of the tear meniscus (maximum peak in 3-minutes versus 1-minute, respectively), however these values are only temporary, balancing rapidly and not finding significant differences at 10 minutes of the study in both eyes. Theoretically, a higher concentration of SH might result in higher water retention, and an increase of TMH would be expected resulting in improvement of dry eye symptoms. However, this assumption was not experienced according to our outcomes. This could be explained by the role of blinking in redistribution of tear volume. Palakuru et al.[24] showed that basal tear volume values were reestablished within five minutes after instillation of artificial tears due to the action of blinking in maintaining a dynamic balance.

This suggests, at least in our study, that a higher concentration of SH only has a transient improvement in the tear meniscus.[25] Within certain limitations, we studied just one type of SH and we did not correlate with other dry eye parameters. Being dry eye a complex disease and tear meniscus reservoir just one of its components, it is difficult to affirm that a higher concentration of SH is not better than a lower one as it is observed in our study. Future research is necessary to correlate different concentrations with other objective and subjective parameters of dry eye. It is also necessary to study with different SH molecules and / or with different molecules and at different concentrations. Regarding the strength, to the best of our knowledge, this is the first study to analyze two different concentrations of the same molecule in a longitudinally manner. Also, we believe we are the first to study tear densitometry.

In conclusion, AS-OCT can be used as a rapid, non-invasive and quantitative method of determining the tear meniscus height, area, depth, density and lower lid meniscus junction in the normal healthy population. 0.2% sodium hyaluronate achieved better TMH and TMA in 1- and 3 -minutes after instillation than 0.1% concentration. However, there were no statistically significant differences between 0.1% and 0.2 % sodium hyaluronate throughout a ten-minute longitudinal profile measurement using DRI-OCT. Future studies in dry eye patients are necessary to validate the application of our findings.

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Figure Legends

Figure 1 – Tear meniscus scans diagram. Side “a” is corneal meniscus junction (CMJ). Side “b” is the lower-lid meniscus junction (LLMJ) and side “c” is tear meniscus height (TMH).

Figure 2 – Tear meniscus sequential changes. A – Before instillation. B – 1-minute after instillation. C – 5-minute after instillation and D – 10-minutes after instillation. Only 0.1% was presented due to similar findings with 0.2% sodium hyaluronate.

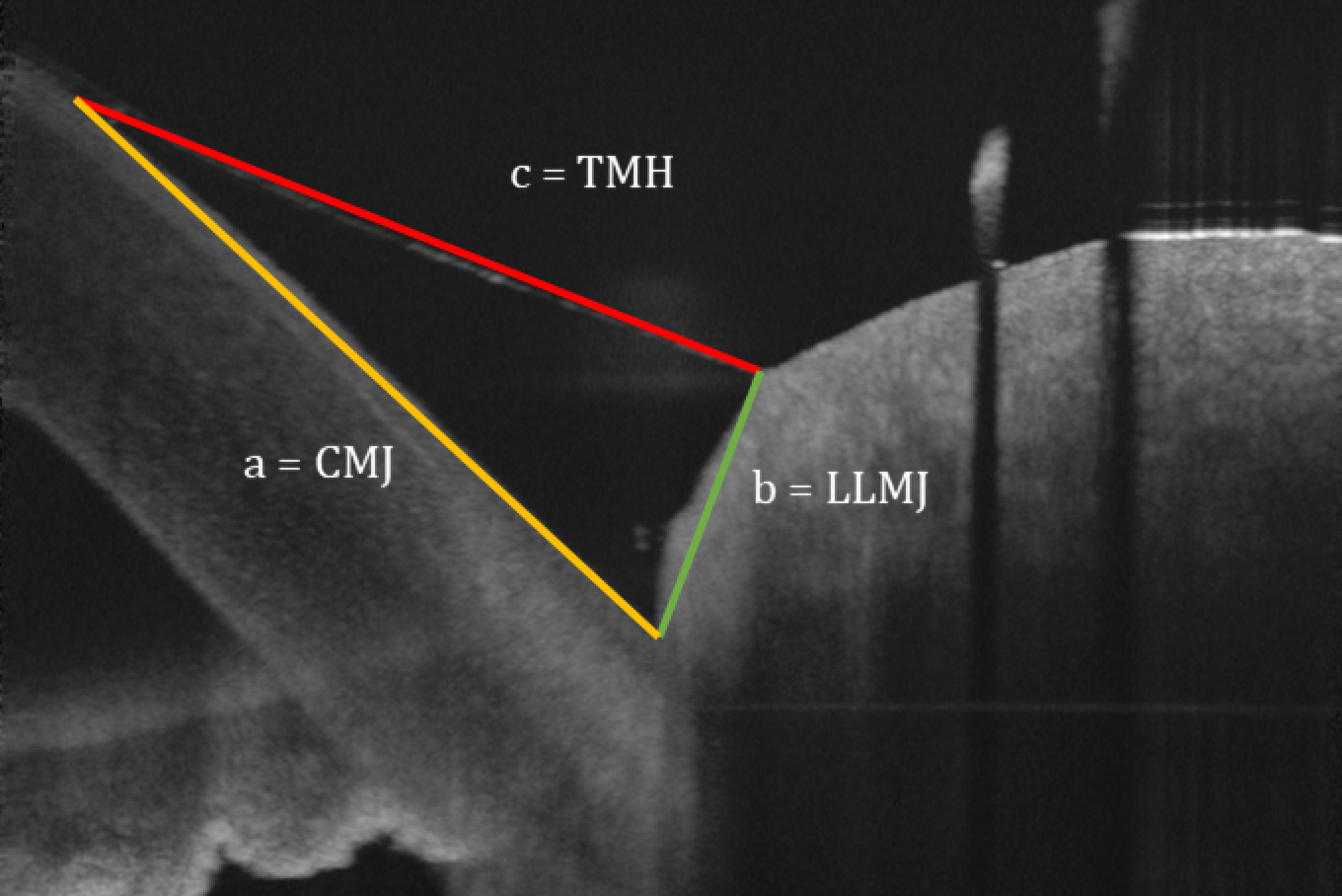
Figure 3 – Tear meniscus height longitudinal changes between 0.1% and 0.2% sodium hyaluronate.

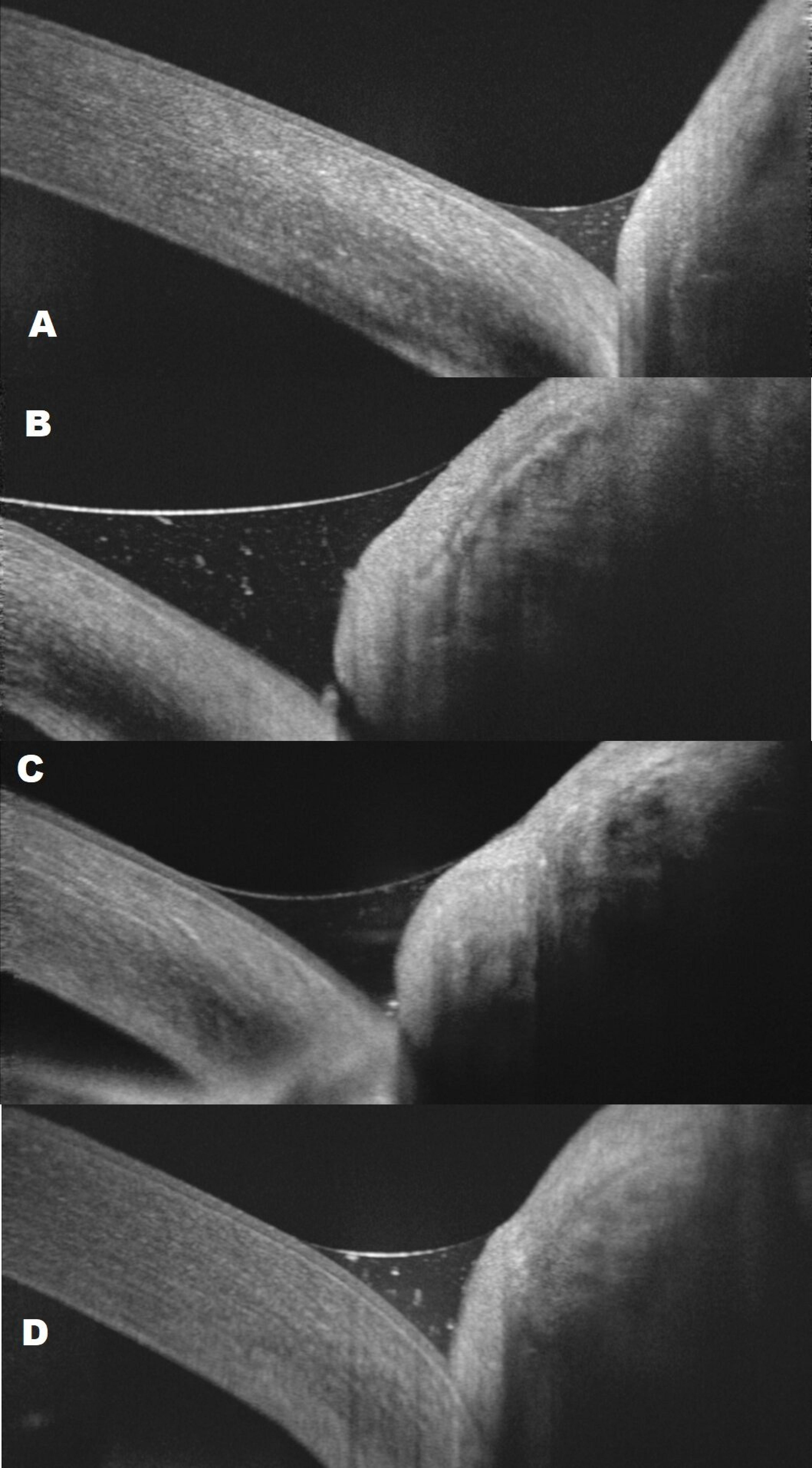
Figure 4 – Tear meniscus area longitudinal changes between 0.1% and 0.2% sodium hyaluronate.

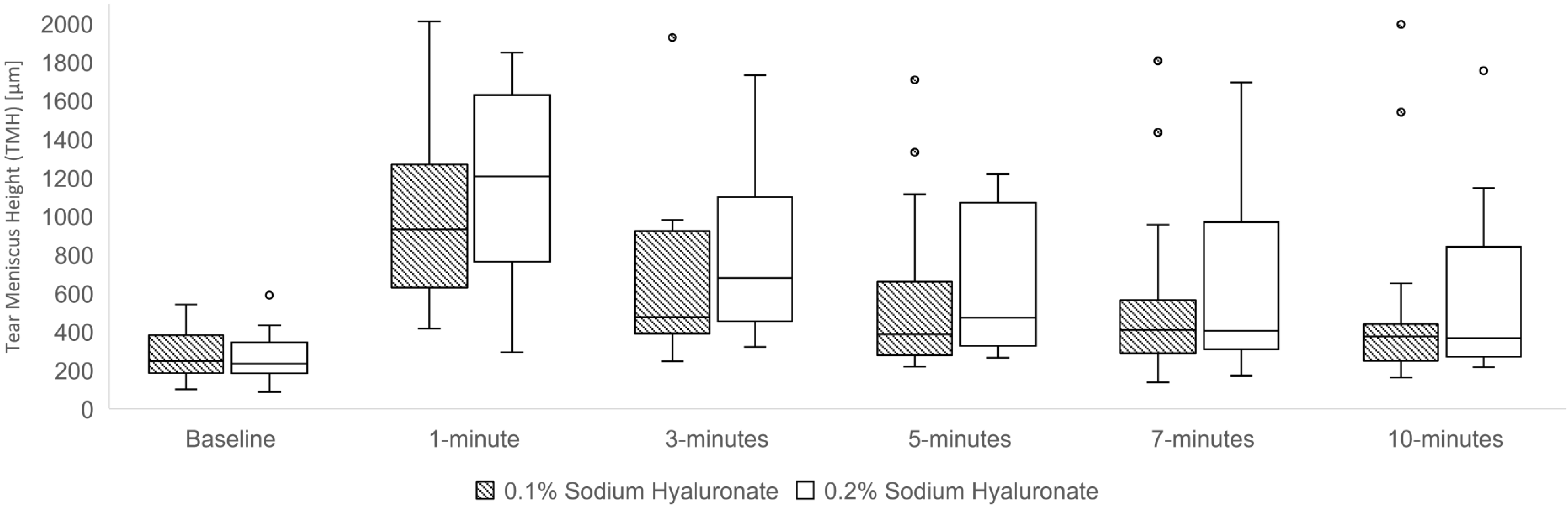
Table 1. Differences between 0.1% and 0.2% sodium hyaluronate group along tear meniscus variables

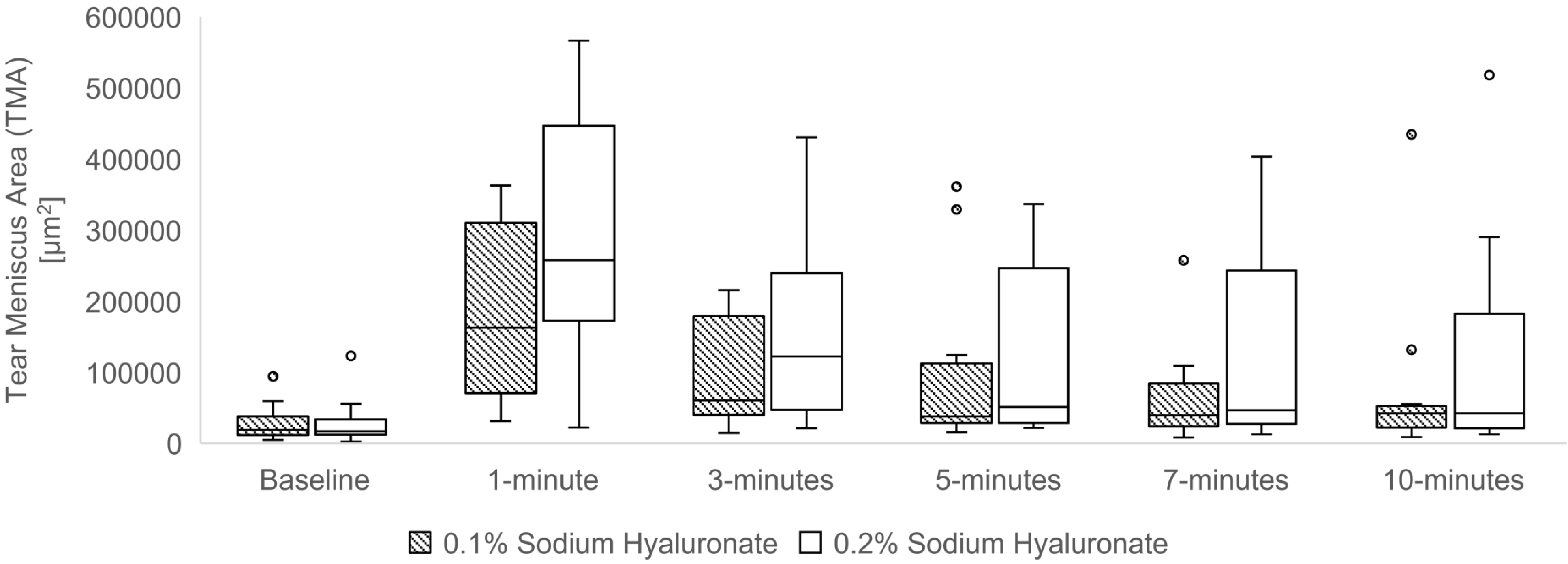
	Group								Mean P value
	0.1% Sodium Hyaluronate				0.2% Sodium Hyaluronate				
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
TMH Baseline	279.94	120.94	100.00	540.00	266.35	123.66	88.00	590.00	.74
TMH 1 min	1,006.65	461.08	417.00	2,011.00	1,196.47	483.08	292.00	1,849.00	.25
TMH 3 min	654.41	411.35	247.00	1,928.00	787.00	433.88	321.00	1,732.00	.36
TMH 5 min	567.88	426.65	219.00	1,708.00	640.59	366.82	265.00	1,220.00	.59
TMH 7 min	547.88	448.73	138.00	1,806.00	617.94	443.81	171.00	1,694.00	.65
TMH 10 min	511.00	493.68	162.00	1,995.00	563.71	420.58	216.00	1,755.00	.74
CMJ Baseline	277.47	114.13	141.00	523.00	284.71	128.39	102.00	645.00	.86
CMJ 1 min	1,000.94	424.46	401.00	1,822.00	1,236.00	530.37	351.00	2,032.00	.16
CMJ 3 min	690.24	448.44	230.00	2,045.00	827.59	453.78	290.00	1,645.00	.38
CMJ 5 min	580.00	422.82	222.00	1,687.00	666.82	411.67	260.00	1,368.00	.54
CMJ 7 min	1,398.65	3,721.16	155.00	15,771.00	637.76	459.30	199.00	1,730.00	.40
CMJ 10 min	515.29	454.06	165.00	1,805.00	579.18	425.90	200.00	1,780.00	.67
LLMJ Baseline	182.82	84.07	74.00	379.00	188.29	89.96	54.00	427.00	.85
LLMJ 1 min	462.24	301.41	122.00	1,208.00	479.12	141.95	153.00	657.00	.83
LLMJ 3 min	309.82	154.33	125.00	741.00	352.44	138.40	133.00	606.00	.41
LLMJ 5 min	304.29	187.27	133.00	745.00	313.71	156.95	156.00	595.00	.87
LLMJ 7 min	306.65	198.93	125.00	856.00	332.71	214.65	125.00	849.00	.71
LLMJ 10 min	276.06	198.72	109.00	905.00	304.35	168.48	116.00	595.00	.65
TMA Baseline	27,484.30	23,950.03	4,477.92	94,005.35	28,428.79	28,610.06	2,375.14	122,675.03	.91
TMA 1 min	273,584.87	297,978.63	30,887.36	1,085,046.39	299,315.89	168,755.66	22,040.75	566,394.04	.75
TMA 3 min	126,359.95	165,942.24	14,251.67	714,013.48	161,842.73	138,776.65	21,284.83	430,407.78	.51
TMA 5 min	115,248.26	165,364.24	15,185.57	616,661.43	120,507.58	116,358.37	21,910.28	336,466.67	.91
TMA 7 min	100,311.77	177,986.78	8,204.25	728,592.49	141,828.70	190,786.28	12,320.50	703,415.57	.52
TMA 10 min	108,119.90	207,908.54	8,532.34	816,402.24	111,480.00	138,104.30	12,516.80	517,871.45	.95
TMD Baseline	70.16	16.56	39.11	99.26	62.31	20.98	30.01	101.26	.23
TMD 1 min	47.70	18.03	29.62	88.95	44.63	10.08	30.01	66.93	.54
TMD 3 min	50.74	11.94	31.65	66.80	54.25	13.49	30.74	78.48	.42
TMD 5 min	53.06	15.54	32.95	93.38	52.44	12.50	33.67	78.29	.90
TMD 7 min	51.87	17.09	32.04	95.41	49.19	8.73	35.28	61.96	.56
TMD 10 min	47.56	12.29	35.35	85.42	50.30	11.59	33.67	73.67	.50

SD: standard deviation; Min: minimum; Max: maximum; TMH: tear meniscus height (µm); CMJ: cornea-meniscus junction (µm); LLMJ: lower-lid-meniscus junction (µm); TMA: tear meniscus area (µm^2); TMD: tear meniscus densitometry (pixels percentage)


c = TMH
a = CMJ
b = LLMJ


A
B
C
D


Tear Meniscus Height (TMH) [µm]
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Baseline
1-minute
3-minutes
5-minutes
7-minutes
10-minutes
0.1% Sodium Hyaluronate
0.2% Sodium Hyaluronate



Tear Meniscus Area (TMA) [µm2]
600000
500000
400000
300000
200000
100000
0
Baseline
1-minute
3-minutes
5-minutes
7-minutes
10-minutes
0.1% Sodium Hyaluronate
0.2% Sodium Hyaluronate