Dynamic Distribution of Artificial Tears on the Ocular Surface

Jianhua Wang, MD, PhD; Peter Simmons, PhD; James Aquavella, MD; Joseph Vehige, OD; Jayachandra Palakuru, MD; Suk Chung, BS; Changyong Feng, PhD

Objective: To study the effects of artificial tear viscosity on tear film thickness, upper and lower tear menisci, and tear volume using optical coherence tomography.

Methods: The central tear film and tear menisci before and immediately after the instillation of different artificial tears were imaged in 40 eyes of 20 healthy individuals. Carboxymethylcellulose sodium, 1.0% (viscosity, 70 cp), propylene glycol, 0.3%, and polyethylene glycol, 0.4% (10 cp), carboxymethylcellulose, 0.5% (3 cp), and isotonic sodium chloride solution (1 cp) were tested on 2 consecutive days. All measurements, including tear film thickness, the height, radius, and area of the tear meniscus, and the estimated tear volume, were obtained at 0, 5, 20, 40, and 60 minutes after instillation.

Results: At instillation, all artificial tears and isotonic sodium chloride solution caused an increase in all tear variables (P < .001). Tear film thickness remained significantly elevated for all drops at 5 minutes (P < .001) and returned to baseline at 20 minutes. Other variables returned to baseline at 5 minutes. Comparing the different drops, tear film thickness and lower meniscus variables at instillation were increased with the more viscous drops (P < .05).

Conclusion: Optical coherence tomography demonstrated that all tear preparations, including isotonic sodium chloride solution, increased tear film thickness for at least 5 minutes and other variables immediately after instillation.

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NORMAL TEAR VOLUME IS ESTIMATED TO BE ON THE ORDER OF 8.5 µL, IN WHICH 4.5 µL IS IN THE CUL-DE-SAC AND APPROXIMATELY 2.9 µL AND 1.1 µL ARE IN THE TEAR MENISCI AND PREOCULAR TEAR FILM, RESPECTIVELY. DYNAMICALLY BALANCED DISTRIBUTION OF THE TEARS MAY BE CRITICAL IN FORMULATING A HEALTHY AND LONG-LASTING TEAR FILM, WHICH PROTECTS THE OCULAR SURFACE DURING EYE OPENING. AS DETERMINED BY INVASIVE METHODS, THE INTERACTION OF THE TEAR MENISCI AND CUL-DE-SAC HAS BEEN REPORTED TO DETERMINE THE STABILITY OF THE TEAR FILM, TEAR VOLUME, AND TEAR Turn-OVER. TEAR VOLUME HAS ALSO BEEN STUDIED BY MEASURING THE LOWER TEAR MENISCUS WITH VIDEOMENOSCIOMETRY THAT USES A BRIGHT LIGHT SHINING ON THE EYE OR VIDEOPHOTOGRAHY WITH THE AID OF FLUORESCIN. NONINVASIVE MEASUREMENTS OF THE INFERIOR MENISCUS HAVE BEEN TAKEN USING A COMMERCIAL OPTICAL COHERENCE TOMOGRAPHY INSTRUMENT. EACH OF THESE STUDIES ATTEMPTED TO CHARACTERIZE THE ENTIRE TEAR FILM SYSTEM BASED ON THE CHANGES IN A SINGLE COMPARTMENT OR BY SNAPSHOT MEASUREMENTS.

ANTERIOR SEGMENT OCT

A real-time corneal OCT, custom developed with the same configurations as described previously, was used to obtain an image of the eye. Briefly, the OCT light source was 1310 nm with a bandwidth of 60 nm. A telecentric optical probe was mounted with a standard slit-lamp. A maximum 15-mm scanning width at up to 8 frames per second was achieved. A
our custom-built OCT was approximately 2 µm.

brief, the repeatability for measuring corneal thickness using tear meniscus variables has been previously documented. In repeatability in measurements of tear film thickness (TFT) and erved interval between 2 image pixels was 12.5 µm. The high isotonic sodium chloride solution (1 cP).

glycerol, 0.4% (10 cP; Refresh Tears; Allergan); and carboxymethylcellulose, 1.0% (70 cP; Refresh Liquigel; Allergan). A randomization table was used to assign the drop sequence.

table include carboxymethylcellulose, 0.5% (3 cP; Refresh Tears; Allergan); and isotonic sodium chloride solution (1 cP).

VISCOSITY OF THE DROPS

We tested 3 different artificial tears and an isotonic sodium chloride solution control (Table). These drops included carboxymethylcellulose sodium, 1.0% (70 cP; Refresh Liquigel; Allergan, Irvine, California); propylene glycol, 0.3%, and polyethylene glycol, 0.4% (10 cP; Systane; Alcon, Fort Worth, Texas); carboxymethylcellulose, 0.3% (3 cP; Refresh Tears; Allergan); and isotonic sodium chloride solution (1 cP).

DROP TEST PROTOCOL

A randomization table was used to assign the drop sequence and resulted in an initial test pair of carboxymethylcellulose, 1.0%, and isotonic sodium chloride solution; and a second pair of carboxymethylcellulose, 0.5%, and propylene glycol, 0.3%, and polyethylene glycol, 0.4%. The pair of solutions was tested in separate eyes (Table) on 2 consecutive days (days 1 and 2) at the same time of day. Later, the same 2 pairs were again tested but in the reverse order. For each solution, the first drop was instilled into the right eye, and then 30 minutes later the pairwise drop was instilled into the left eye. These imaging sessions were staggered between eyes to facilitate the imaging on both eyes. Each drop in each eye was followed up for 60 minutes. It took approximately 1.5 hours to complete each visit.

OUTCOME MEASURES

Five outcome measures were obtained at each visit. These measures included central TFT, 3 tear meniscus variables around the upper and lower eyelids, and total estimated tear volume. The tear meniscus variables included the upper tear meniscus radius (UTMR), upper tear meniscus height (UTMH), upper tear meniscus cross-sectional area (UTMA), lower tear meniscus radius (LTMR), lower tear meniscus height (LTMH), and lower tear meniscus cross-sectional area (LMTA). The 8 images, corresponding to 1 second of time, immediately after a full blink, were used to yield these variables. Data from 2 interblink intervals at each time were averaged. Total tear volume was calculated as detailed later.

STUDY PROCEDURE

To establish baseline variables before any drops were added, a vertical 12-mm OCT scan was performed across the central cornea (apex) while the study participant blinked normally. The OCT imaging was repeated immediately and at 5, 20, 40, and 60 minutes after instillation of 35 µL of the designated artificial tear or isotonic sodium chloride solution control by a pipette. These imaging sessions were staggered between eyes to facilitate the imaging of both eyes. During the break between OCT imaging, the participant was asked to sit in the laboratory while an audio reminder set to blink at 10 blinks per minute was played to facilitate as much as possible the participant’s control of the blink rate. After the 60-minute follow-up with the 2 less viscous solutions (carboxymethylcellulose, 0.3%, and isotonic sodium chloride solution), 1 drop of gel (GenTeal; Novartis Pharmaceuticals, East Hanover, New Jersey) was instilled into the eye, followed by OCT imaging. This procedure highlighted the interface between the cornea and the tears and facilitated the measurement of true corneal thickness (Figure 1) for the calculation of TFT. With the more viscous artificial tears (carboxymethylcellulose, 1.0%, and propylene glycol, 0.3%, and polyethylene glycol, 0.4%), there was no need to use the gel because we were able to obtain true corneal thickness immediately after the instillation of these drops (Figure 2).

IMAGE PROCESSING

Custom software was used to process the OCT images to obtain these results. To avoid the distortion due to the central specular reflex of each image, the central 30 pixels (0.39-mm width) were removed. After that, a reflectivity profile (Figure 1D) was generated from the central 21 axial scans of 8 consecutive images immediately after blinking. The combined thickness,
including the cornea and TFT, was defined as the distance between the first and last peaks, and true corneal thickness without the tear film was defined as the distance between the first and last peaks. The TFT was determined indirectly by subtracting the corneal thickness obtained after the instillation of carboxymethylcellulose, 1.0%, and propylene glycol, 0.3%, and polyethylene glycol, 0.4%, or the gel after instillation of carboxymethylcellulose, 1.0%, and polyethylene glycol, 0.4%, the tear film is marked by the red asterisk. Greater tear menisci were present immediately after instillation of all 4 solutions (B–E). The larger increases of TFT (red asterisk) were with carboxymethylcellulose, 1.0% (B) and propylene glycol, 0.3%, and polyethylene glycol, 0.4% (C). Tear film thicknesses in panels A, D, and E were calculated as detailed in the “Image Processing” subsection of the “Methods” section.

TEAR VOLUME ESTIMATION

Total tear volume was estimated from upper and lower tear menisci and TFT based on some assumptions. The tear film volume was calculated by multiplying the TFT times 250 mm², the average exposed surface area. Because the tear meniscus height seems not to be uniform across the eyelid, with the largest value in the center, a factor of 3/4 was used to calculate the tear volume in the tear menisci according to a previous study. An eyelid length of 25 mm was used as a constant to complete the calculation of total tear volume on the ocular surface. The complete equation was as follows:

\[
\text{TFT} \times 250 \text{ mm}^2 \times \left( \frac{3}{4} \right) = \text{Total Tear Volume on Ocular Surface}
\]

STATISTICAL ANALYSIS

Data analysis was conducted using a statistical analysis software package (Statistica; StatSoft Inc, Tulsa, Oklahoma). Repeated-measures analysis of variance was used for overall effects, and post hoc paired t tests were used to determine any pairwise differences (P < .05).

RESULTS

Between the 2 successive measurements during the study period, no significant differences were found in any of the measured variables and estimated tear volume with all 4 drops (repeated-measures analysis of variance, P = .58). Immediately after the instillation of artificial tears and isotonic sodium chloride solution, all variables increased significantly (post hoc tests, P < .001; Figure 3 and Figure 4). After that, the values recovered to baseline with no significant differences after 20 minutes (Figure 3A-H).

Among the drops studied, carboxymethylcellulose, 1.0%, and propylene glycol, 0.3%, and polyethylene glycol,
Figure 3. Measured variables of tear distributions over time with 3 artificial tears and the control. Mean results from successive measurements of both eyes were plotted in panels A through H. A, Significant increases of tear film thickness (TFT) occurred immediately after instillation and remained at 5 minutes ($P < .001$). Carboxymethylcellulose sodium, 1.0%, and propylene glycol, 0.3%, and polyethylene glycol, 0.4%, induced significantly greater increases of TFT than carboxymethylcellulose, 0.5%, and isotonic sodium chloride solution. At 5 minutes, no differences were found among the drops, although the TFT remained elevated compared with baseline ($P < .001$). B, Immediately after instillation, estimated tear volume increased significantly with all drops ($P < .001$), with the highest increase by carboxymethylcellulose, 1.0%. At 5 minutes, the increases by carboxymethylcellulose, 1.0%, and propylene glycol, 0.3%, and polyethylene glycol, 0.4%, were significantly different from baseline. C, For the upper tear meniscus radius, no differences were found among drops over time. D, For the lower tear meniscus radius, carboxymethylcellulose, 1.0%, induced significantly greater increases ($P < .001$) immediately after instillation compared with the other solutions. At 5 minutes and afterward, no differences were found among drops. E, For the upper tear meniscus height, propylene glycol, 0.3%, and polyethylene glycol, 0.4%, induced a greater increase immediately after instillation compared with carboxymethylcellulose, 1.0% ($P < .001$). At 5 minutes and afterward, no differences were found among drops. F, For the lower tear meniscus height, carboxymethylcellulose, 1.0%, induced significantly greater increases ($P < .001$) immediately after instillation and at 5 minutes compared with the other solutions. After that, no differences were found among drops. G, For the upper tear meniscus cross-sectional area, propylene glycol, 0.3%, and polyethylene glycol, 0.4%, induced a greater increase immediately after instillation than carboxymethylcellulose, 1.0% ($P < .001$). At 5 minutes and afterward, no differences were found among drops. H, For the lower tear meniscus cross-sectional area, carboxymethylcellulose, 1.0%, induced a significantly greater increase ($P < .001$) immediately after instillation compared with others. At 5 minutes and afterward, no differences were found among drops. Vertical bars denote 95% confidence intervals.
0.4%, induced significantly higher TFT than carboxymethylcellulose, 0.5%, and isotonic sodium chloride solution immediately after instillation (post hoc tests, \( P > .05 \)). At 5 minutes, no significant differences were found in TFT among drops (post hoc tests, \( P > .05 \)), although the increases due to all drops were significantly compared with baseline (Figure 3A). Immediately after instillation, carboxymethylcellulose, 1.0%, induced a significantly greater increase in estimated tear volume compared with others. At 5 minutes, no significant differences among drops were found (post hoc tests, \( P > .05 \)), whereas carboxymethylcellulose, 1.0%, and propylene glycol, 0.3%, and polyethylene glycol, 0.4%, remained significantly higher than baseline (Figure 3B).

No differences were found in UTMR among drops over time (Figure 3C). Carboxymethylcellulose, 1.0%, induced significantly greater LTMR immediately after instillation compared with others, and by 5 minutes and afterward, no differences were seen among the drops (Figure 3D). Propylene glycol, 0.3%, and polyethylene glycol, 0.4%, induced a greater increase in UTMH immediately after instillation than the others (\( P < .001 \)), and at 5 minutes and afterward, no differences were seen among drops (Figure 3E). Carboxymethylcellulose, 1.0%, induced significantly greater LTMH immediately after instillation compared with others and at 5 minutes compared with carboxymethylcellulose, 0.5%, and isotonic sodium chloride solution (Figure 3F). Propylene glycol, 0.3%, and polyethylene glycol, 0.4%, induced greater UTMA immediately after instillation than carboxymethylcellulose, 1.0% (\( P < .001 \)), but by 5 minutes and afterward, no significant differences were found (Figure 3F). Carboxymethylcellulose, 1.0%, induced significantly greater LTMA immediately after instillation compared with others (Figure 3H).

Immediately after instillation of the 4 solutions, TFT (Figure 4A), tear volume (Figure 4A), LTMR (Figure 4B), LTMH (Figure 4C), and LTMA (Figure 4D) were strongly correlated with the viscosity of tested artificial tears. However, variables of the upper tear meniscus (B–D) were not well correlated with viscosity. Note the different scales in each plot from A through D. Vertical bars denote 95% confidence intervals.
carboxymethylcellulose, 0.5%, which was equal to iso-
tonic sodium chloride solution (Figure 4B-D). The
dominant component of the estimated total tear volume
of the ocular surface was the lower meniscus (Figure 2
and Figure 3).

**COMMENT**

The present study reports on the development and use
of real-time anterior segment OCT to evaluate the
dynamics of the tear-film cycle, particularly in relation
to the effect of different artificial tear formulas. A cus-
tom OCT device was used to capture cross-sectional
images of the entire interpalpebral ocular surface at
approximately 8 times per second. To our knowledge,
this is the first time that multiple variables indicating
tear distribution and dynamics after adding artificial
tears were obtained simultaneously. This study, there-
fore, provides baseline variables for further modeling
the tear system. Real-time scanning and recording of the
OCT as used in this study enable continuous imaging
of the tears and dynamic distribution on the
ocular surface. In particular, blinks can be tracked and
the conditions before and after the blink can be studied.
Because this system uses a nonvisible scan light and no
materials other than the test fluid are added to the eye,
it minimizes reflex tearing and the disturbance of the
tear system. A wide scan with a telocentric optical
design ensures simultaneous imaging of both upper and
lower tear menisci and of the tear film itself. This
enables us to better understand the tear system. For
instance, from the captured images after instillation of
carboxymethylcellulose, 1.0% (Figure 2), the lower tear
meniscus seems to extend considerably farther forward
across the mucocutaneous junction. This observation
might change the conventional view about the role of
the mucocutaneous junction, which has been thought
to be the limit of the lower tear meniscus.

The repeatability of OCT imaging in the measure-
ment of corneal thickness and tear dynamics has previ-
ously been reported. With approximately 2 µm of
repeatability in the measurement of total thickness of
the cornea and tear film,11 the OCT used in this study
is expected to reliably detect the change of TFT after
the instillation of artificial tears. This finding confirms
observations by Zaki et al17 and Wilson,18 who found that in-
creasing the viscosity of instilled fluid slowed the fluid
clearance. One of the findings of the present study was
that changes in central TFT and lower tear meniscus di-
ensions were correlated with the viscosity of the arti-
ficial tear, but the dimensions of the upper tear menis-
cus were not. These results indicate that other factors,
such as specific gravity or wetting characteristics of the
artificial tear, may be more important in determining the
fluid held along the upper lid. The upper lid has a ten-
dency to lose fluid owing to gravity and travel distance,
and it also moves more rapidly than the lower lid during
blinking.

Hydraulic connectivity between the upper and lower
menisci might also explain our results. In this model, the
2 menisci are hypothesized to be connected via the lat-
eral canthus with free flow between them. If this is the case,
then the relationship between the upper and lower radii
can be deduced as follows. By approximating the shapes
of the upper and lower menisci as cylinders, the pres-
sures relative to atmospheric pressure of the upper (P_{UTM})
and lower (P_{LTM}) menisci are given by the following:

\[ P_{UTM} = -T/UTMR \]
\[ P_{LTM} = -T/LTMR \]

where \( T \) is the surface tension and UTMR and LTMR
are the radii of the upper and lower menisci, respectively.

If there is free flow between the 2 menisci, the pressure
difference between them should be given by the following:

\[ P_{LTM} - P_{UTM} = \Delta h \times d \times g / T \]

where \( \Delta h \) is the height difference between upper and
lower meniscus, \( d \) is the density of the tear film, and \( g \) is
the acceleration due to gravity. Combining these 3 equa-
tions yields the following:

\[ 1/UTMR = 1/LTMR + \Delta h \times d \times g / T \]

Immediately after instillation of carboxymethylcellu-
lose, 1.0% (Figure 3C and D), the radius of the LTMR is
approximately 0.3 cm, and the surface tension is approxi-
mately 45 dynes/cm, the height difference is 0.8
\( \left( T \right) \) cm (Figure 3E and F), the density is 1 g/cm³, and the
acceleration is 981 cm²/s. Solution of the final equation gives
a UTMR of 0.0481 cm (481 µm), which is close to the
observed value in Figure 3C. Furthermore, if the LTMR is
reduced to half of that value, 0.15 cm (corresponding roughly
to the value observed for propylene glycol, 0.3%,
and polyethylene glycol, 0.4%), the predicted reduction
in the UTMR is relatively small (eg, 481-415 µm). Thus,
this model seems to explain why relatively large vari-
ations in the LTMR cause relatively little variation in the
UTMR.

This study has some limitations and possible mea-
surement errors. No midviscosity was selected for the
quantitation of the effect on dynamic tear distribution.
Additional studies on this might be warranted. Another
limitation could be that the true corneal thickness for the
calculation of tear film was obtained at different times
with different tested drops. With less viscous drops, the
true corneal thickness was obtained after the 60-minute
follow-up. With the more viscous drops, it was ob-
tained immediately after the instillation of the tested drops.

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\end{align*}
This might induce possible measurement errors because corneal thickness might alter during the study period. From the data shown in Figure 3A, the alteration of the corneal thickness during such a short period seems to be little because the TFTs at 60 minutes were similar with all 4 drops. Furthermore, the values were almost identical to those at baseline. This possible error could be simply eliminated by applying the gel to all tested drops. Other factors that contribute to possible errors in this method have been discussed previously.10,11 Reflex tearing in the opposite eye might be induced during instillation of the artificial tears in the test eye. The tearing effect can be discounted because each drop was tested twice, once as the first drop and again as the second drop on each study participant.

In summary, OCT is a promising method for studying the tear system and the effect of viscosity of artificial tears. Immediately after drop instillation, tear viscosity was correlated with the TFT, the lower tear meniscus, and the estimated tear volume. However, no effect was seen 20 minutes after drop instillation.

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REFERENCES


From the Archives of the Archives

It is evident that penicillin F did not cause any damage to the retina or other parts of the interior of the eye when 1,000 units was introduced. Penicillin X was well tolerated in the dose of 2,000 units. Circumscribed lesions of the retina, as observed with the preparations of penicillin G used in this series, were absent. When the dose of penicillin X was increased to 5,000 units, there was a localized area of injury in the neuroepithelium in 1 of 4 eyes. The retina was unchanged after injections of 2,000 units of commercial crystalline sodium penicillin.