The Ocular Protection Index

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Abstract: The interaction of the time between blinks, or the interblink interval (IBI), and tear film breakup time (TFBUT) helps to regulate the integrity of the ocular surface. A protected surface exists when the TFBUT matches or exceeds the IBI. In contrast, an unprotected surface exists when TFBUT is less than the IBI. This is clinically relevant because repeated intermittent exposure of a tear film–deficient cornea can lead to ocular discomfort and the development of clinical signs, such as keratitis and redness. The relationship between TFBUT and IBI has been quantified by the Ocular Protection Index (OPI), which is calculated by dividing TFBUT by IBI. If the OPI is <1.0, the patient has an exposed ocular surface, putting them at risk for the development of the signs and symptoms of dry eye, whereas if the OPI is ≥ 1.0, the patient's ocular surface is tear film protected. The OPI has proven to be useful in assessing the factors that may cause or exacerbate dry eye. This review discusses the development and use of the OPI model, its relationship to dry eye, and factors that are known to alter blink rate and tear film integrity.

Key Words: Ocular Protection Index, dry eye, keratoconjunctivitis sicca, clinical trials, tear film breakup time, blink rate, interblink interval

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Dry eye is characterized by a disturbance in tear film physiology that leads to a clinically evident drying of the ocular surface. Multiple underlying pathologic conditions can result in altered tear production and integrity, resulting in or exacerbating dry eye disease and conditions. Environment and visual tasking are also known to affect the signs and symptoms of dry eye. Clearly, both the lids and tear film are responsible for providing protection to the ocular surface. Therefore, the number of seconds quantifying a patient's tear film breakup time (TFBUT) provides insufficient pathophysiologic information for the clinician to fully understand the nature and severity of the case of dry eye. The Ocular Protection Index (OPI) was developed to quantify the interaction between blinking and the tear film, providing a framework to assess the effects of tear film instability associated with dry eye. This review will discuss the development and clinical relevance of the OPI model and its relationship to dry eye, as well as factors known to alter blink rate and tear film integrity.

HISTORY OF THE OPI

Standardization of TFBUT

TFBUT has traditionally been measured with large and varying amounts of sodium fluorescein ($\sim$50 μL or more). By using this technique, TFBUT was determined to be $\geq$10 seconds in patients with normal ocular health and $<$10 seconds in patients with dry eye.

Using sodium fluorescein in amounts that exceed the average tear volume (known to be $\sim$6 or 7 μL[1]) is thought to influence tear film stability and artificially lengthen TFBUT. The accuracy and reproducibility of TFBUT has been shown to be improved by using well-controlled microquantities of sodium fluorescein (1–5 μL).[2,3] With this improved technique, more reliable and reproducible reference values have been established for the clinician, where TFBUT is $\geq$5 seconds in healthy patients (mean = 7.1 $\pm$ 1.17 seconds) and $<$5 seconds in patients with dry eye (mean = 2.2 $\pm$ 0.82).[4]

Relationship Between TFBUT and Ocular Discomfort

A relationship between ocular discomfort and TFBUT was discovered as a result of the refinement in TFBUT technique. Studies have shown that $\sim$73% patients with a positive diagnosis of dry eye experience ocular discomfort within 1 second of when an examiner reports TFBUT.[5] In addition to suggesting a noninvasive method for determining tear film stability (symptomatic break-up time [SBUT]), these data indicate that the manifestation of ocular discomfort after tear breakup may be responsible for stimulating the eye to blink.

Significance of the Blink

Blinking plays a primary role in the protection of the ocular surface by assisting in the removal of debris from the tear film and aiding in the discharge of meibomian gland secretions into the tear film. Blinking is the primary mechanism responsible for the maintenance of the integrity of the ocular surface, because blinking facilitates the distribution and the formation of the tear film across the corneal surface.

Reported mean blink rate values vary greatly, and an assessment of various studies suggests that the average blink rate might be in the vicinity of 8.0 blinks/min.[6] This would yield a mean interblink interval (IBI), the time between

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complete blinks, of roughly 7.5 seconds. Blink rate is greatly variable and is strongly influenced by external factors, psychologic and physiologic influences, and activity-related factors. Natural, involuntary blinks can be categorized as: a twitch blink, consisting of a small flutter of the upper lid, an incomplete blink, in which the upper lid covers less than two thirds of the cornea, and a complete blink, where the upper lid covers more than two thirds of the cornea. Only a complete blink is successful at completely redistributing the tear film across the ocular surface.

To be properly measured, blink rate evaluation techniques must be standardized and noninvasive to avoid disruption of the natural saccades of blinks. Researchers have developed a precise method for measuring blink rate that uses a digital micro-camera and an infrared illuminator that tracks the diameter of the pupil. This allows for only complete blinks to be counted, defined as blinks where the upper lid covers 95% of the cornea. Because many activities and environmental conditions impact blink rate, patients are isolated and complete a standardized visual task during the evaluation.[7]

One Integrated System

A lack of consensus existed on the interpretation of TFBUT and its clinical significance, despite the improved reliability and reproducibility of the test. After identifying the relationship between ocular discomfort and TFBUT, as well as standardizing the measurement of TFBUT and blink rate, the significance of blink rate on the TFBUT system was recognized. The interaction between TFBUT and IBI assists in maintaining the health of the ocular surface, preventing ocular surface injury and the formation of the symptoms of dry eye.

In an ideal system, the TFBUT would match or exceed the IBI, ensuring that the ocular surface would remain protected. In contrast, an unprotected ocular surface exists when TFBUT is less than the IBI. The larger the interval between tear film breakup and the following blink, the greater potential for damage to occur to the ocular surface. As the TFBUT blink system repeats over the course of the day, the potential for damage to occur exponentially increases. The discordance between TFBUT and IBI can be worsened by factors that shorten TFBUT or by factors that lengthen the IBI.

OPI CALCULATION

The OPI was developed to quantify the interaction between TFBUT and the IBI. The OPI is calculated by dividing TFBUT by the IBI, as shown in the formula below:

$$\text{Ocular Protection Index (OPI)} = \frac{\text{Tear Film Break-Up Time (TFBUT)}}{\text{Inter-Blink Interval (IBI)}}$$

An OPI score <1.0 (OPI < 1.0) is considered unfavorable because the patient has an exposed ocular surface, resulting in the development or exacerbation of the signs and symptoms associated with dry eye, whereas an OPI score ≥ 1.0 is considered favorable because the patient has a tear-protected ocular surface, potentially resulting in fewer dry eye signs and symptoms. This quantitative approach is useful in measuring clinically relevant alterations in the TFBUT blink system that cause tear film instability and the signs and symptoms of dry eye.

Changes in OPI can be quantified by performing a binomial analysis assessing 2 possible clinically significant outcomes: success, where TFBUT either matches or exceeds the IBI (a calculated OPI ≥ 1.0), and failure, where TFBUT remains shorter than the IBI (a calculated OPI < 1.0). Therefore, in addition to its usefulness as a diagnostic tool, OPI can measure the changes in the patient's dry eye severity over time and can evaluate the effect of dry eye treatments in promoting tear film stability.

FACTORS THAT ALTER BLINK RATE AND THE IBI

The blink system, which uses multiple muscle groups and neurologic pathways to function, can be greatly affected by the interaction of external and internal factors that might, on first review, seem insignificant.

Environmental Conditions

Alterations in temperature, humidity, lighting conditions, and airflow have a profound affect on blink rate. The controlled adverse environment (CAE)[8] is a model that has become widely accepted as a standardized method in the drug development process. It is currently used both to screen patients for inclusion into clinical trials and is a way of producing standardized stress to the ocular surface, providing a precise methodology for evaluating a relative effectiveness of both prophylactic and therapeutic agents.[9–12] The CAE provides reproducible environmental challenges by controlling humidity ($<10\%$), temperature ($76 \pm 6°F$), airflow (constant, nonturbulent), lighting conditions, and visual tasking (television or PC use), and can significantly increase blink rate in patients with dry eye.[13] Changes in blink rate from environmental conditions may be attributed to a compensatory mechanism triggered by increased discomfort.

Cognitive Activities, Visual Tasks, and Emotional States

Blink rate can change depending on the activity being completed. The frequency of blinking can increase during conversation, whereas intently focusing on a visual task can cause blink rate to drop. Resting blink rate is estimated to be between 8 and 21 blinks/min, whereas blink rate is at its greatest during conversation, during which the average range is from 10.5 to 32.5 blinks/min (or 19–26 blinks/min according to a more specific estimate).[14,15] Conversely, the rate of blinking while reading has been shown to decrease to an average of 4.5 blinks/min.[15] Use of computers has also been shown to significantly decrease blink rate.[16] Studies evaluating blink rate suggest that people blink during line changes while reading, in anticipation of the next stimulus presentation, or at times when mental load is at its lowest.[17–19] Blink frequency has also been shown to change during alteration in gaze direction and while squinting.[20–22]

Emotions can also modulate blink rate. One study observed increased blink rate in people experiencing emotional excitement, anxiety, or frustration, whereas another study

found that guilt alters blink rate.[23,24] Although the impact of mental processes and the neural pathways controlling blink rate are not fully understood, blink rate changes may be altered by cognitive and emotional function.[25]

Diseases and Medications

Dopamine levels in the central nervous system are thought to be associated with the motor movements that control blinking. Diseases associated with abnormal dopamine levels have been found to alter blink rate.[26] A decreased blink rate is found in patients with Parkinson disease, whereas patients with schizophrenia exhibit an increased blink rate.[27] Patients with diabetes have been shown to have significantly lower blink rates than nondiabetic patients.[28] Lid retraction can occur in patients with thyroid ophthalmopathy, causing incomplete blinks that fail to distribute tears across the ocular epithelium.[29] Blepharospasms and ptosis may also alter blinking, hindering the spread of the tear film across the surface of the eye. Systemic medications can alter blink rate by directly affecting the nerves responsible for blinking. Medication suspected to influence blinking includes psychoactive drugs, muscle relaxants, and thyroid medications.

Ocular Surface Conditions

Pathologic conditions, such as dry eye, have been shown to increase blink rate.[30] Studies have correlated TFBUT and IBI, suggesting that tear film instability is detected by the cornea, initiating the blink sequence to restore the tear film.[31,32] Research has shown that an alteration in corneal sensitivity can affect blink rate.[31] One study found that subjects with dry eye with reduced corneal sensitivity blinked 3.2 times/min, a reduction of ~57% compared with healthy subjects. In contrast, subjects with dry eye with normal corneal sensitivity blinked an average of 10.3 times/min, almost twice as frequently as subjects without dry eye with normal corneal sensitivity.[33] The ability of the highly innervated cornea to detect changes in tear film stability and ocular surface conditions seems to be a major driving force behind blink rate.

FACTORS THAT AFFECT TFBUT

Diseases Associated With Dry Eye

The prevalence of mild-to-moderate dry eye is estimated to be 11%–22% of the general population.[34] There is an increased prevalence of dry eye symptoms reported by women, increasing in frequency with age and menopause status.[35–37] Research has shown that lacrimal gland and meibomian gland functions are significantly affected by sex and sex hormones.[38]

Sjögren syndrome is the most well-known disease known to affect the aqueous layer of the tear film through its autoimmune-initiating lacrimal gland damage. Sjögren syndrome is also associated with a higher frequency of meibomian gland dysfunction, which affects the tear film lipid layer and can lead to excess evaporation.[39] Sjögren syndrome can be a primary ocular disease or be associated with other connective tissue autoimmune diseases such as rheumatoid arthritis and lupus erythematosis. Non-Sjögren syndrome dry eye may result from congenital or acquired lacrimal gland dysfunction, sarcoidosis, human immunodeficiency virus (HIV), graft-versus-host disease, obstruction of the lacrimal ducts, or reflex hypersecretion.[40]

Evaporation of the tears can occur when there is a deficiency in the lipid layer of the tear film.[41] Decreased lipid release into the tear meniscus can be brought on by squamous lid margin metaplasia and keratinization and breakdown of the lid margin epithelium. Insufficient lipid secretion can also be caused by aplasia of the meibomian glands, blepharitis, meibomitis, or obstructive meibomian gland disease. Lid abnormalities, such as ectropion, entropion, or irregular lid margins, and contact lens wear may also contribute to hyperevaporation. Sex hormones, innervation, and vascularization are influential factors responsible for regulating meibomian gland function—as a probable result, meibomian gland disease has been reported as a major factor in the dry eye that occurs during menopause.[42,43] Loss of goblet cell function caused by chronic inflammation, vitamin A deficiency, chemical burns, or cicatrizing conjunctival disorders may impede mucous layer formation.[44,45]

Drying Effects of Systemic Medications

Many systemic medications adversely influence the eye-altering tear flow and production or combining of natural components of the tear film.[46,47] Ocular discomfort can result from changes in tear film stability resulting from the use of systemic medications. Oral antihistamines, antihypertensives, antiemetics, antidepressants, and diuretics have been shown to cause or exacerbate dry eye.[48]

In particular, 1 common complaint associated with use of oral antihistamines is the "drying effect." Muscarinic receptors, specifically the M_3 subtype, regulate the secretion of protein and fluid in the eye.[49] H_1 receptor–blocking antihistamines have been reported to reduce aqueous output of the lacrimal gland and decrease mucous output of the goblet cells, thereby altering tear film integrity.[40,41,43] Studies have shown that clinically meaningful damage to the ocular surface, measured in the form of increased corneal and conjunctival staining, decreased TFBUT, and increased ocular discomfort, occurs after dosing with systemic antihistamines in subjects with normal ocular health.[50,51] Furthermore, this damage increases in a dose-dependent manner.[44]

Effect of the Environment

Regardless of the etiology, environmental factors can greatly influence the signs and symptoms of dry eye. In the northeast United States, the greatest frequency of reports of dry eye–related ocular discomfort occurs in the winter months, when subjects are exposed to considerably more forced air (in the form of indoor heating) than they are in the summer months (in the form of air conditioning).[52] Individuals with normal ocular health may experience the symptoms of dry eye when exposed to adverse conditions, such as arid or windy environments (for instance the conditions on an airplane), or while performing visual tasks such as using a computer. Changes in tear production have been seen in subjects exposed to the CAE model. This model standardizes environmental conditions including humidity, airflow, lighting, temperature, and visual tasking to exacerbate the signs and symptoms of dry eye.[8] One study investigated the time to natural

compensation, defined as the point at which a temporary improvement in ocular discomfort scores during CAE exposure was observed. In this study, healthy subjects took ~10 minutes to naturally compensate, whereas subjects with mild-to-moderate dry eye took an average of 20 minutes, and subjects with severe dry eye did not exhibit natural compensation.[53] Healthy subjects possess the ability to reflex tear, a compensatory mechanism to alleviate ocular discomfort and prevent ocular surface damage. In contrast, the ability to reflex tear is diminished or absent in subjects with dry eye, indicating a deficiency in the compensatory mechanism.

CLINICAL RELEVANCE OF OPI

Indication of Severity of Dry Eye

OPI may be used as a diagnostic tool to assess a patient's risk in developing the signs and symptoms associated with dry eye. The OPI is clinically relevant because intermittent exposure of a tear film–deficient ocular surface leads first to ocular discomfort and to the development of keratitis and redness. OPI not only provides a dichotomous snapshot of the risk of exposure but also evaluates the severity of the patient's dry eye condition according to the degree of discordance between TFBUT and IBI, allowing for the identification of patients who are the most susceptible to the signs and symptoms of dry eye.

Educational Tool

Patient education is a crucial step to the successful management and treatment of dry eye. Informing patients of the interaction between their tear film integrity and their blinking patterns helps patients to become conscious of their blinking and artificial tear use when exposed to adverse environments or intense visual tasking.

A patient can also independently monitor his or her dry eye condition under different circumstances and evaluate the ability of treatments to relieve his or her symptoms with use of the SBUT, in which the patient looks straight ahead while the time from last blink to first ocular awareness is recorded. The SBUT has been shown to be within ~1 second of TFBUT for most patients with dry eye.[8]

Treatment Effect

The juxtaposition of blink rate against TFBUT allows for the observation of clinically significant changes and allows for measurement of the effects of artificial tears or therapeutic agents on ocular surface protection. In addition, by using the SBUT, patients can estimate changes in their own tear film integrity after the use of a therapeutic agent.

Clinical Research Endpoint

In clinical research, identification of the target patient population is crucial to a study's success. In addition, clinical endpoints must be relevant, precise, reproducible, and have appropriate scales to detect changes produced by the treatment. The OPI allows for identification of subjects who have an unprotected ocular surface and therefore are at risk for the development of the signs and symptoms of dry eye. The OPI provides a means to quantify a therapeutic agent's effect on tear film stability. If the therapeutic agent is successful, TFBUT either matches or exceeds IBI, providing protection to the ocular surface. If the therapeutic agent is ineffective, TFBUT remains shorter than the IBI. Therefore, a successful therapeutic agent that provides protection to the ocular surface will improve a deficient OPI score (OPI < 1.0) to an OPI ≥ 1.0. Precise measurement of TFBUT by using microquantities of fluorescein and noninvasive blink rate are crucial to evaluating treatment effects by using the OPI.

The effectiveness of OPI as a clinical endpoint has already been supported by a study comparing 3 marketed tear substitutes. This was a crossover study in a population of 50 patients with dry eye that measured OPI at 5, 10, 15, 20, 30, 45, and 60 minutes after instillation. Significant differences were found between treatments at various time points.[54]

CONCLUSIONS

The OPI provides a quantifiable measurement of the interaction of the tear film integrity and blink process in protecting the ocular surface from damage and preventing the development of the signs and symptoms associated with dry eye. The OPI is a clinically relevant tool that has proven useful in assessing factors that cause or exacerbate dry eye and in evaluating therapeutic agents that may improve tear film stability.

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