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Animal Models of Dry Eye Disease- A Review

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Abstract:
A number of patient suffering from dry eye disease is increasing daily, subsequently increase the need of proper medication to treat the symptoms and eventually improve the patient's condition. Thus the need arise for proper animal and non-human primate animal model of the disease, which would serve the purpose of understanding disease in the better physiological setting and medication for treating dry eye disease. This review article focus on some animal models disease like monkey, rabbit, rat, mice, dog and mouse which are generally used for carrying out studies on dry eye symptoms in research lab and industry worldwide. This paper also gives guidance toward the mechanistic and traditional model of dry eye disease and help researchers in deciding a particular relevant model for their own purpose.

Key words: Dry eye disease, Animal model, Schirmer paper strips, Tear secretion**.**

INTRODUCTION

Dry Eye Syndrome, which has been recently termed as Dry Eye Disease (DED) is the most frequent disorder in Ophthalmology. [1] Dry eye can also be known as Keratoconjunctivitis sicca (KCS), either due to insufficient tear production or excessive tear evaporation, both resulting in tear hyperosmolarity that leads to symptoms of discomfort and ocular damage.[2-3] Dry eye syndrome is a prevalent disease that affects visual acuity, activities of daily living, and quality of life. A number of contributory factors affect the severity of dry eye syndrome, including autoimmune disease, environmental surroundings, contact lens use, hormonal changes, anatomical features, chronic inflammation, infections, and iatrogenic factors, such as medications or surgery.[4]

The modern definition of dry eye disease is based on the concept of the three layers of the tear film.[5] Secondary factors such as pathological changes to the eyelids, cornea, or conjunctiva, can themselves disturb the normal function of the tear film. Neurotransmitters, hormones, and immunological processes play an important role in the regulation of the tear production by the lacrimal gland. [6-7] Various environmental factors like contact lenses, pollution, working at video display terminals can affect the tear film.[8]

Symptoms Dry Eye Disease [2,9] are like dry sensation, foreign body or "gritty" sensation, redness-blurred vision, irritation/redness, contact lens intolerance, mucous discharge-burning/stinging and increased frequency of blinking-tearing.

PREVALENCE

No authentic prevalence survey has been conducted in India but it is noted that out of the patients above the age of 30 years attending the outdoor, one out of every four has a complaint pertaining to dry eye. In a community study in Sweden the prevalence rate of 15% was found in the general population aged 55-72 years. [2]

A recent survey conducted in year 2007 based upon a well characterized population of adult men and women in the USA identified a prevalence of 5 to 30 percent at various age groups. These rates extrapolate to potentially 9.1 million dry eye patients in USA alone. About 5 million Americans above 50 years of age have mild to moderate dry eye disease.[9] In women at the age of 45 to 52 when menopause usually sets in, an imbalance occurs between the estrogen and androgen hormone due to decrease of androgens after the menopause. Decrease in androgen levels, excites inflammation in lachrymal gland and ocular surface, disrupting the normal homeostatic maintenance of the lacrimal gland and ocular surface. [10-11]

DIFFERENT ANIMAL MODEL FOR DRY EYE

Different animal model used in dry eye disease like monkey, rabbit, rat, mice, dog and mouse for Measurement of tear secretion, measurement gland secretion, measurement of tear production, measuring tear film stability, tear film instability, corneal uptake measurement and for ocular surface staining.

Monkey

Schirmer paper strips have been used in squirrel monkeys for tear secretion detection after the surgical removal of the main lacrimal gland. [12] In this case, the application time has been 5 min, similar to the test performed in humans, but no other details have been provided.

Rabbit

Because of the globe size, testing with the standard filter paper seems to be appropriate also in the rabbit model of dry eye, but so far the procedure has not been standardized**.** In the two rabbit models developed by closing the meibomian gland orifices [13] and closing the lacrimal gland excretory duct together with the removal of the nictitating membrane and harderian gland, [14] the schirmer test has been performed with topical proparacaine, but no data have been provided about the duration of the test and the lid aperture.

In a model of dry eye based on 1.0% atropine sulfate instillation to decrease neurological stimulation for tear secretion, [15] the Schirmer test was performed with standard filter papers for 3 min without anesthesia, showing a reduction in value from 20.57±1.26 to 13.51±1.36 mm 36 mm after two days of this treatment. Recently, in an autoimmune dacryoadenitis rabbit model,[16] the Schirmer test performed for 1 min provided a basal value of 8±1 mm, while 3 weeks later the value declined to 4 mm. Because of the great variability in Schirmer test conditions in rabbits, such as the duration of the test, comparisons are difficult, and the need for a standard especially is high. We suggest that a test of 1 min without use of anaesthetics has a high chance of achieving acceptable reproducibility.[17-19]

Rat

In rat models of dry eye also used because of the small globe size, the Schirmer test requires changes. For example, have used cut Schirmer strips (1×17 mm) for 1 min in their rat model of dry eye developed by surgically removing the exorbital lacrimal gland. Unfortunately, while they have reported an overall decrease in tear production of 50% compared to normal values, they have not shown the exact amount, and therefore it is not useful for future comparisons of the Schirmer test in rat.[20]

Mice

In a study conducted on the MRL/lpr mouse model of dry eye disease for measurement of tear secretion, the filter paper has been adapted by cutting a 0.5×3.0 mm strip, and placing it under the lower lid near the medial canthus for 2 min. [21] Interestingly, the length of wetting has been read at 10× Magnification using a micrometer on a dissecting microscope, thus providing an accurate measure of the paper wetting. Using this technique, values of 2.8 ±0.2 and 3.1×0.3 mm, in males and females, respectively, showed non-statistically significant differences with control straining values. [22]

Dog

In dogs, the test can be performed using the same paper used for humans, but the duration of the test has been limited to 1 min to make it more practical. In normal dogs, the Schirmer without anaesthesia value is 20±4 mm $min^{-1,}$ [23] while following topical anaesthesia it is 11.6±6.1 mm min^{-1}. [24] In the spontaneous canine KCS, an animal model of dry eye widely used to study KCS pathology and to test new therapies, [24] Schirmer values under 10 mm min^{-1} without anaesthesia are considered significant when associated with corneal ulceration, pigment deposition on the corneal surface, and mucopurulent conjunctivitis. In the dog, the Schirmer test has shown a decrease of 10–37% after extirpation of the lacrimal gland alone, and 29–57% after removal of the third eyelid gland. Interestingly, in both cases no consequences on the ocular surface epithelium have been demonstrated. [26]

Mouse

In the MRL/MpJ-fas^{lpr}/fas^{lpr} (MRL/lpr mouse model of dry eye disease, the cotton thread test has been used instead of the filter paper to measure tear production [27] In particular, a cotton thread prestained for 2 mm with fluorescein was applied for 2 min. A significant difference for both male and female MRL/lpr mice has been shown as compared to normal BALB/c mice, but the authors have not provided specific values. It has to be pointed out that in the two studies on the MRL/lpr model [21,27] the tear secretion was evaluated under systemic anaesthesia, and the substance and dose used differed in the two reports. Since it is well known that anaesthesia can significantly influence tear production in humans, as in animals, [28-29] it is difficult to interpret these data although they are often referenced as valid outcomes measures in these murine models.

CONCLUSION

For studying special causes of dry eye, such as defects of neuronal reflex loops, environmental changes, or evaporative dry eye, the model of choice should recapitulate the underlying pathophysiologic mechanism. The well being patient depend on research and treatment measures. Although the animal model might be lack certain parameter and certain type of validity, they can be surely used and improved for prediction and treatment of Dry Eye Disease.

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