Rear 4-minute Schirmer Test, A Modified Indicator of Schirmer Test in Diagnosing Dry Eye

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Abstract

This study was designed to find a reliable and convenient indicator (a modified Schirmer test) to improve the accuracy of assessing tear secretion and diagnosing dry eye. This is a prospective continuous study on 180 volunteers. Schirmer test I without anesthesia was performed once on both eyes to determine the value of normal Schirmer test. The values of tear secretion were recorded in each minute. Examined individuals also underwent other examinations: the standard patient evaluation of eye dryness (SPEED), the Ocular Surface Disease Index (OSDI), fluorescein stain, tear film breakup time (BUT), and Meibomian gland (MG) grading. The participants were divided into two groups: dry eye (DE) group and non-dry eye (ND) group. The mean age was 39.41 ± 14.05 years in DE group and 37.62 ± 13.17 in ND group. The value of 2-minute Schirmer test, 3-minute Schirmer test, 4-minute Schirmer test and 5-minute Schirmer test was 5.36 ± 4.63 , 5.57 ± 2.11 , 7.21 ± 4.13 and 10.93 ± 6.30 respectively in DE group. And these indicators were 8.25 ± 6.80 , 2.73 ± 2.31 , 7.36 ± 3.42 , 11.84 ± 6.16 in ND group. The 4-minute ST has significant correlation with OSDI and SPEED in DE group ($r = -0.242 / -0.183$) and in ND group ($r = -0.316 / -0.373$). Meanwhile, 4-minute ST had stronger connection with fBUT ($r = 0.159$) and MG ($r = -0.162$) in DE group. And 4-minute ST also had higher accuracy in diagnosing severe dry eye and borderline dry eye. The 4-minute Schirmer test may be a supplement indicator in assessing tear secretion and diagnosing dry eye.

Introduction

Dry eye (DE) is a common disorder in ocular surface and now the number of the patients is increased rapidly. The incidence of DE varies from 5% to 35%¹⁻² due to geographical and ethnic differences. There are about 30 million persons with DE in the world³. According to the International Dry Eye Workshop in 2017, DE is defined as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles"⁴.

The stable tear film has been considered as the key to healthy ocular surface because it can protect the lubricated environment for eyes⁵. When tear film becomes abnormal, patients often have the six main symptoms: dry, gritty or sandy, burn, appear red, crust forms on lashes and eyelids stick shut in the morning⁶. The assessment of people's feelings is a major component for the diagnosis of DE. However, it's unfortunate that signs of the disease do not always correlate with symptoms. In that case, we need objective ocular examinations. The most common diagnostic tests include Schirmer test (ST)⁷⁻⁸, tear breakup time (BUT)⁴, corneal fluorescein staining (CFS)⁹, tear meniscus height¹⁰.

ST was used as a diagnostic test for dry eye syndrome in 1903 and it can help to evaluate the tear volume¹¹. In clinical practice, a special filter paper is placed at the middle and lateral thirds of the lower fornix with or without anesthesia⁸. After 5 minutes, the tear secretion of person can be measured by the wetting paper. ST is always performed just one time in clinical practice. However, ST has several serious disadvantages such as discomfort, irritation, low reproducibility, requiring long time and inconvenience¹²⁻¹³. Because of these limitations, many efforts were made to improve the ST's efficiency and comfort, just like to be performed this test after using anesthesia or changing the filter paper¹⁴. But these changes may not make significant improvements. With anesthesia, a reflex component was still alive and it may mislead physician to judge the situation of examinee. We set out this research for increasing the applicability and convenience of ST. Our purpose was to find a reliable and convenient way about ST which is more connected with the symptom of DE and help ophthalmologists diagnose DE.

Materials And Methods

1. Subjects

This prospective study was performed at the outpatient clinic of the Second Affiliated Hospital of Zhejiang University School of Medicine in September of 2019. All subjects were divided as DE groups and non-dry eye (ND) groups. The criteria of DE diagnosis was OSDI higher than 13 points and fBUT shorter than 10 seconds and non-dry eye diagnosis was OSDI was not higher than 13 points or fBUT were not shorter than 10 seconds. The exclusion criteria were subjects who were under 18 years old and pregnancy, with eye allergies, conjunctival inflammation, corneal ulcer, eyelid inflammation, palsy, valgus and other ocular lesions, history of wearing contact lenses within 30 days, history of intraocular operation within 6 months, severe blepharitis, or severe systemic disease. This study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine(NO. 2019-307). All individuals who agreed to enter this study provided written informed consent after explanation of the nature and possible consequences of the study.

2. Dry eye symptom questionnaires

2.1. The ocular surface disease index(OSDI)

The ocular surface disease index (OSDI) was a validated dry eye questionnaire that can measure the severity of DE, symptoms, functional problems, and environmental triggers queried for the past week ¹⁵. Each answer of OSDI in 12 questions was graded on a scale of 0-4. A total OSDI scores ranged from 0-100.

2.2. The standard patient evaluation of eye dryness (SPEED) questionnaire

The standard patient evaluation of eye dryness (SPEED) questionnaire was administered to grade the level of dry eye symptomology ¹⁶. The assessment standard of the SPEED questionnaire is derived by summing the scores from the frequency and severity parts of the questionnaire of 3 months. The value for each part of the frequency and severity questions in the SPEED questionnaire were obtained by summing the 0–4 scores of each of the 8 items and the total SPEED scores ranged from 0–28.

3. Dry eye symptom examinations

3.1. Schirmer test I

Schirmer test (ST) was performed once without topical anesthesia. In each test, both eyes were tested at the same time. The filter paper (Showa Yakuhin Kako Co, Ltd, Tokyo, Japan) was folded and placed between the lower eyelid and the globe at the junction between the middle and lateral thirds of the eyelid. The participants were asked to close their eyes, as since ST with close eyes may be more reliable in DE ¹⁷. The test lasted 5 minutes and the length of wetted paper was directly read off the scale on the paper. Wetting was measured in eyes at 1, 2, 3, 4, and 5 minutes. The participants were excluded from the study if any of the scores exceeded 30 mm (the whole paper was wetted) because of inability to give an exact measurement of the amount of wetting. Results were interpreted as follows: ≤ 5 mm as severe dry eye, ≤ 10 mm as borderline dry eye and >10 mm as normal tear secretion ¹⁸. We observed multiple indicators of Schirmer test as following:

1.ST1: the value of normal Schirmer test.

2.2-minute ST: the value of first 2 minutes of Schirmer test.

3.rear 3- minute ST: the value that five minute's value subtracting first two minutes of ST

4.rear 4-minute ST: the value that five minute's value subtracting first minute of ST

3.2. tear film breakup time(BUT)

Tear film instability was assessed using BUT measurements, which were obtained using the following method. TBUT test include fluorescein tear film break-up time (fBUT) and noninvasive tear film break up time (NIBUT). fBUT: Fluorescein was added to the tear film for both eyes and patients were asked to blink several times to ensure that it was uniformly distributed across their eyes. The time from the last blink of the eye to the first dry spot on the tear film was measured. Three consecutive measurements were made and recorded. The average values of three measurements were recorded. NIBUT: NIBUT were measured by Keratograph 5M (Oculus Optikgerate GmbH, Wetzlar, Germany). The examinee should place the lower jaw on the jaw rest and keep both eyes open. After successful focusing, examinee should blink 2 times and look at the red point in the center, keeping the eye open as much as possible until the next blink. Then the device can automatically detect the tear film distribution map and displays the measured value. The results of the BUT measurements were categorized as moderate (5–10s) or severe (<5s) ¹⁹⁻²⁰.

3.3. Meibomian gland grading (MG grading)

The quality of the Meibomian gland dropout was briefly assessed using a Meibomian Gland Evaluator (TearScience, Morrisville, NC, United States). A total of 15 Meibomian glands (in the nasal, middle, and temporal parts of the lower tarsus, respectively) were selected. The quality of Meibomian dropout was graded as follows: 0, clear fluid; 1, thick and cloudy dropout; 2, inspissated and congealed dropout with the consistency of toothpaste; 3, none present. The total scores ranged from 0–45.

3.4. Corneal fluorescein staining score(CFS)

Corneal fluorescein staining score assessment was used to stain the patients' corneas in this study. The cornea was divided equally into five quadrants of and the score for each quadrant was recorded after fluorescein staining, as follows: 0, no punctate staining; 1, less than 30 stained points; 2, more than 30 stained points but no fusion; 3, entirely stained with fusion. A total score of five part was given as 0–15.

4. Statistics

All statistical analyses were performed using SPSS software (version 24, IBM, Armonk, NY, United States) for Mac. The chi-square test and Pearson's rank-order correlation were used to identify the correlation between ST, BUT, OSDI, SPEED, MG grading and CFS. An independent sample t-test was used to compare the parameters of the ST indicators. One- way ANOVA test was used to compare the values of indicators in two groups. Figures were created by SPSS and GraphPad Prism, version 8 (San Diego, CA). Descriptive statistics were summarized as mean $\pm$ standard deviation (SD). A p-value < 0.05 was considered statistically significant.

Results

1.Participants Demographics and Baseline characteristics

A total of 360 eyes of 180 Chinese persons were included in this study. The 120 participants were diagnosed as DE, while 60 participants were not in the situation of DE. Table 1 shows the baseline characteristics of the subjects. The objective examinations results of NIBUT, fBUT, MG grading and CFS in DE group were 4.70 ± 2.28 , 3.69 ± 2.22 ,

22.51±11.68 and 0.88±0.25, respectively. And the results in ND group were 8.43±3.31, 4.22±2.20, 16.32±9.60 and 0.35±0.06, respectively. The scores of OSDI and SPEED were 30.12±12.91, 12.59±4.63 in patients and 6.62±3.35, 5.27±2.87 in ND group. No age significant difference was detected between DE and ND group. Other dry eye related indicators had significant difference between two groups ($p \leq 0.01$).

2. Schirmer Test and dry eye group

2.1 Comparison among the different value of Schirmer test

In this study, the participants were asked to perform one time ST and various ST indicators were compared. These indicators were different statistically with each other in both groups. Figure 1 summarizes four indicators of ST in DE group. The value of ST1, 2-minute ST, rear 3 minutes ST and rear 4 minutes ST was 10.93±6.30, 5.36±4.63, 5.57±2.11 and 7.21±4.13 respectively in DE group. The four indicators were statistically different with each other ($p \leq 0.01$). Significant positive correlations were observed between ST1, 2-minute ST, rear 3 minutes ST and rear 4 minutes ST. The details were listed in Table 2. We also recorded the ST results at each minute. However, we noticed a sign of Schirmer Test. The speed of mean wetting per minute had been slow down in ST. The speed was about 1.25-4.56 mm per minute in test including DE group and ND group (Figure 2). We found that the speed in the first minute was unstable and casual. Therefore, we focused on the other indicators of ST which removed the data of the first minute. We observed that the value of rear of 4-minute was about 3/5 of ST1.

2.2 Different value of Schirmer test and Dry eye symptom questionnaires

We analyzed the relationship between four indicators and Dry eye symptom questionnaires. We found that these indicators all had correlation with OSDI or SPEED. Table 3 showed the details. We found that both ST1 and rear 4-minute ST had relationship with other indicators. To our surprise, we noticed that the correlation of ST and questionnaires had low relationship.

2.3 Different value of Schirmer test and other dry eye examinations

BUT was the most convenient diagnostic test used in the clinical practice. The subjects were performed three consecutive fBUT tests and one time NIBUT under this research. Besides BUT, MG grading and CFS were performed. All four tests had statistical significance between DE group and ND group. Meanwhile, we investigated the correlation about different values of ST and other 4 tests. The results showed the relationship between different ST and fBUT, MG grading, and CFS in Table 3.

3. Schirmer Test and non-dry eye group

We also collected the data of non-dry eye group. The value of ST1, 2-minute ST, rear 3 minutes ST and rear 4 minutes ST was 11.84±6.16, 8.25±6.80, 2.73±2.31, 7.36±3.42, respectively in ND group (Figure 3). The four indicators were statistically different with each other ($p \leq 0.01$) in ND group. The score of OSDI and SPEED was 6.62±3.35 and 5.27±2.87. Other dry eye tests like NIBUT, fBUT, MG grading and CFS were 8.43±3.31, 4.22±2.20, 16.32±9.60 and 0.35±0.06. Table 4 shows the correlation between ST and other examinations in ND group.

4. rear 4-minute ST may be a suitable supplement for dry eye diagnosis

In order to evaluate four indicators in diagnosing DE, the true positive rate (TPR) was compared. The TPR of ST1, 2-minute ST, rear 3 minutes ST and rear 4 minutes ST was 101 eyes (42.08%), 75 eyes (31.25%), 68 eyes (28.33%), and 145 eyes (60.41%). We also calculated the true negative rate (TNR) in ND group. We found that the TNR of ST1, 2-minute ST, rear 3 minutes ST and rear 4 minutes ST was 50 eyes (41.67%), 47 eyes (39.17%), 48 eyes (40.00%), 54

eyes (45.00%). Statistically, TPR of four indicators had significant difference ($p < 0.001$). According to the above results, we chose one indicator, 2-minute ST, to be a reliable supplement for ST. We found that the number of patients in theory whose tear secretion was less than 10 mm in 5 minutes accounts for 74.62% of persons which the value of rear 4-minute ST is lower than 6 mm. To provide the reference for the clinical diagnosis, we divided the patients into severe dry eye ($ST \leq 5$ mm) and borderline dry eye ($5 \text{ mm} < ST \leq 10$ mm). We compared rear 4-minute ST with ST1 in subjective questionnaires and objective examinations. Table 5 illustrated the points.

Discussion

Nowadays, there is still no consensus on the diagnostic criteria of DE in different areas, even though The International Dry Eye Workshop has declared the rules of diagnosis of DE. In previous reports, it's known that most ocular examinations are not perfect means to diagnose DE²¹. The sensitivity and specificity in detecting symptoms are too low to meet people's need. One of the major reasons may be the heterogeneity of DE. However, there is no single existing test to diagnose DE reliably. Two or three tests are required to meet our need to diagnose DE. It means we need more time and more work. All we can do is to simplify the process and improve the accuracy of tests.

ST is one of the most commonly used test for assessment of ability in tear production for its low cost and simplicity. However, the value for diagnosing DE has not yet been unified with the improvements of ST over decades. Jones'¹² prospective of basal ST was that the cut-point should be set at 10mm per 5 minutes, however, Van Bijsterveld²² thought the length of wetting paper less than 5.5mm should be defined as deficient aqueous production. And it's recommended currently that a cut-off 5.0mm per 5 minutes is meaningful^{4,23}. Even though ST without topical anesthesia may make patients feel discomfort, we think that reflex tear secretion is an indispensable indicator.

ST is easily influenced by many factors like reflex tear, paper irritation, temperature and humidity²⁴⁻²⁵. Therefore, we have been in the process of improving the accuracy of ST in the long term of clinical practice. In Vasileios Karampatakis' research, he compared the 2- and 5-minute test and evaluated the reliability and the tear secretion of the Schirmer test I in 2 minutes²⁶. And we saw a similar sign about the speed of wetting. During the initial 1 minute, the speed of tear production was faster than the next minutes, this phenomenon suggested an adaptation of the central nervous system²⁷. Besides, another reason was that a little of remaining tears may exist in the lower fornix. For that matter, the doctor should make sure that there is no tears before the test. But we realized that the technique and process of dipping tears was not inconvenient for doctors and patients. In the long term, ST is implemented only once in clinical practice. Only one test may impair the accuracy of results and the validity of the test. In our study, we took the ST once as usual and recorded the values of each minute in order to get the elements that may be more reliable to assess the tear secretion. We noticed that the research of Vasileios Karampatakis just got a conclusion of tear secretion in most normal individuals. Our study included patients and normal persons. Therefore, we had enough samples to verify whether our selected indicator really works or not.

As we known, ST without topical anesthesia may induce reflex tearing and the reflex tear secretion is unstable. Because of this reason, we need to investigate tear secretion of every minute in patients. Therefore, we selected four indicators: ST1, 2-minute ST, rear 3 minutes ST and rear 4 minutes ST. In our study, the ST values were consistent with the OSDI and SPEED. But the relevance was low. At the same time, we valued ST with other examinations like BUT, MG grading and CFS. BUT is considered to be the most common statistical pattern to value the stability of tear film²⁸. MG grading is used to assess the capacity of secreting the lipids and the extent of gland obstruction. The abnormality of meibomian gland including morphology and block may cause the problems of lipid layer²⁹. Fluorescein staining score is a test that value the environment of cornea. An unhealthy tear film may impair the function of epithelial cell and

induce keratitis. Just like the results above, ST and rear 4-minute ST were correlated to the fBUT and MG grading in DE group. And rear 4-minute ST was correlated to the fBUT and MG grading in ND group. It suggested that participants in our study, no matter which group, rear 4-minute ST may be a reliable indicator in assessing tear secretion.

To increase the accuracy of examination's, we should take care of more than one indicator. The rear 4-minute test was chosen as a safe time limit for the evaluation of normal tear secretion. In first minute test, the reflex tear secretion irritated by Schirmer strip was biggest. And Vasileios Karampatakis suggested that the speed of wetting strips may decrease after 2 minutes due to the evaporation of paper²⁶. Besides ST1, we noticed an interesting phenomenon that rear 4-minute may be a supplement way to value the condition of ocular surface. And it also had strong relationship with other DE tests. Last but not least, rear 4-minute ST had higher accuracy in diagnosing DE. It just need few second to record the value of ST and it's able to give a reliable data to evaluate the tear secretion. But there are some participants who may be sensitive about the paper and have a massive tear secretion. These persons are not fit this measurement and need other tests.

In conclusion, our study found that rear 4-minute ST seemed a better supplement measurement to value the tear production. In our opinion, it's most likely to be DE patients when the figure of rear 4-minute ST is less than 6mm and 5-minute ST less than 10mm. One of the limitations of this study is that we did not account for the drainage and evaporation of tears. And we need more clinical practices for our indicator.

Declarations

Due to technical limitations, Declarations Section is not available for this version.

References

1. Chen W, Li J, Zheng Q. Prevalence and risk factors of dry eye disease among a hospital-based population. *Invest Ophthalmol Vis Sci* **54**:935. DOI: [10.1097/ICL.0000000000000064](https://doi.org/10.1097/ICL.0000000000000064) (2013)
2. Hashemi H, Khabazkhoob M, Kheirkhah A, et al. Prevalence of dry eye syndrome in an adult population. *Clin Exp Ophthalmol*. Apr;**42**(3):242-8. doi: 10.1111/ceo.12183. DOI: [10.1111/ceo.12183](https://doi.org/10.1111/ceo.12183) (2014).
3. Phadatare SP, Momin M, Nighojkar P, Askarkar S, Singh KK. A comprehensive review on dry eye disease: diagnosis, medical management, recent developments, and future challenges. *Adv Pharm*. 2015:704946. DOI: [10.1155/2015/704946](https://doi.org/10.1155/2015/704946). (2015).
4. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. **15**(3):276-283. doi: 10.1016/j.jtos.2017.05.008.(2015).
5. King-Smith PE, Begley CG, Braun RJ. Mechanisms, imaging and structure of tear film breakup. *Ocul Surf*. **16**(1):4-30. doi: 10.1016/j.jtos.2017.09.007. (2018)
6. Bandeen-Roche K, Muñoz B, Tielsch JM, West SK, Schein OD. Self-reported assessment of dry eye in a population-based setting. *Invest Ophthalmol Vis Sci*. **38**(12):2469-75.(1997)
7. SalehTA, McDermottB, BatesAk,EwingsP. Phenol red thread test vs. Schirmer's test: a comparative study. *Eye (Lond)*. **20**(8):913-5. doi: 10.1038/sj.eye.6702052.(2006)
8. Bawazeer AM, Hodge WG. One-minute Schirmer test with anesthesia. *Cornea*.**22**(4):285–7. DOI: [10.1097/00003226-200305000-00001](https://doi.org/10.1097/00003226-200305000-00001). (2003)
9. Feenstra RPG, Tseng SCG. Comparison of fluorescein and rose bengal staining. *Ophthalmology*. **99**(4):605-17. DOI: [10.1016/s0161-6420\(92\)31947-5](https://doi.org/10.1016/s0161-6420(92)31947-5) .(1992)

10. García-Resúa C, Santodomingo-Rubido J, Lira M, Giraldez MJ, Vilar EY. Clinical assessment of the lower tear meniscus height. *Ophthalmic Physiol Opt.* **29**(5):487-496. doi: 10.1111/j.1475-1313.2009.00634x. (2009)
11. Schirmer O. Studien zur Physiologie und Pathologie der Tranenabsonderung und Tranenabfuhr. *Graefes Arch Clin Exp Ophthalmol.* **56**:197–291. (1903)
12. Jones LT. The lacrimal secretory system and its treatment. *Am J Ophthalmol*, **62**(1):47-60. DOI: [10.1016/0002-9394\(66\)91676-x](https://doi.org/10.1016/0002-9394(66)91676-x).(1966)
13. Masmali A1, Alqahtani TA, Alharbi A, El-Hiti GA. Comparative Study of Repeatability of Phenol Red Thread Test Versus Schirmer Test in Normal Adults in Saudi Arabia. *Eye Contact Lens.* **40**(3):127-31. doi:10.1097/ICL.000000000000025.(2014)
14. Halberg GP, Behrens C. Standardized Schirmer tear test kit. *Am J Ophthalmol.* **51**:840-2. DOI: [10.1016/0002-9394\(61\)91827-x](https://doi.org/10.1016/0002-9394(61)91827-x).(1961)
15. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye Work Shop (2007). *Ocul Surf.* **5**(2):93-107. DOI: [10.1016/s1542-0124\(12\)70082-4](https://doi.org/10.1016/s1542-0124(12)70082-4).(2007)
16. Ngo W, Situ P, Keir N, Korb D, Blackie C, Simpson T. Psychometric properties and validation of the Standard Patient Evaluation of Eye Dryness questionnaire. *Cornea.* **32**(9):1204-10. doi: 10.1097/ICO.0b013e318294b0c0.(2013)
17. Serin D1, Karsloğlu S, Kyan A, Alagöz G. A Simple Approach to the Repeatability of the Schirmer Test Without Anesthesia: eyes open or closed? *Cornea.* **26**(8):903-6. DOI: [10.1097/ICO.0b013e3180950083](https://doi.org/10.1097/ICO.0b013e3180950083). (2007)
18. Vashisht S1, Singh S. Evaluation of Phenol Red read test versus Schirmer test in dry eyes: A comparative study. *Int J Appl Basic Med Res.* **1**(1):40-2. doi: 10.4103/2229-516X.81979.(2011)
19. Kashkouli MB, Alemzadeh SA, Aghaei H, Pakdel F, Abdolalizadeh P, Ghazizadeh M, et al. Subjective versus objective dry eye disease in patients with moderate-severe thyroid eye disease. *Ocul Surf.* **16**(4):458-462. doi: 10.1016/j.jtos.2018.07.003. (2018)
20. Sang X, Li Y, Liu Y, Liu JH, Wang XR, et al. Lipid layer thickness and tear meniscus height measurements for the differential diagnosis of evaporative dry eye subtypes. *Int J Ophthalmol.* **11**(9):1496-1502. doi: 10.18240/ijo.2018.09.11. eCollection 2018.(2018)
21. Lin PY1, Cheng CY, Hsu WM, Tsai SY, Lin MW, Liu JH, Chou P. Association between Symptoms and Signs of Dry Eye among an Elderly Chinese Population in Taiwan: The Shihpai Eye Study. *Invest Ophthalmol Vis Sci.* **46**(5):1593-8. DOI: [10.1167/iovs.04-0864](https://doi.org/10.1167/iovs.04-0864).(2005)
22. Van Bijsterveld OP. Diagnostic tests in the sicca syndrome. *Arch Ophthalmol.* **82**(1):10-4. DOI: [10.1001/archopht.1969.00990020012003](https://doi.org/10.1001/archopht.1969.00990020012003). (1969)
23. Danjo Y. Diagnostic usefulness and cutoff value of Schirmer's I test in the Japanese diagnostic criteria of dry eye. *Graefes Arch Clin Exp Ophthalmol.* **235**(12):761-6. DOI: [10.1007/BF02332860](https://doi.org/10.1007/BF02332860). (1997)
24. Kallarackal GU, Ansari EA, Amos N, et al. A comparative study to assess the clinical use of fluorescein meniscus time (FMT) with tear break up time (TBUT) and Schirmer's tests (ST) in the diagnosis of dry eyes. *Eye (Lond).* **16**(5):594-600. DOI: [10.1038/sj.eye.6700177](https://doi.org/10.1038/sj.eye.6700177). (2002)
25. Tsubota K. The importance of the Schirmer test with nasal stimulation. *Am J Ophthalmol.* **15**,111(1):106-8. DOI: [10.1016/s0002-9394\(14\)76908-9](https://doi.org/10.1016/s0002-9394(14)76908-9).(1991)
26. Karampatakis V1, Karamitsos A, Skriapa A, Pasiadis G. Comparison Between Normal Values of 2- and 5-Minute Schirmer Test Without Anesthesia . *Cornea.* **29**(5):497-501. doi: 10.1097/ICO.0b013e3181c2964c.(2010)
27. Rhoades RA, Tanner GA. Medical Physiology. Philadelphia, PA: Lippincott, Williams & Wilkins. 2003.
28. Mcmonnies CW. Tear instability importance, mechanisms, validity and reliability of assessment. *J Optom.* **11**(4):203-210. doi: 10.1016/j.optom.2017.11.004. (2018)

29. Pucker AD, Nichols JJ. Analysis of meibum and tear lipids. *Ocul Surf*. **10**(4):230-50. doi: 10.1016/j.jtos.2012.07.004. (2012)

Tables

Table 1 Baseline characteristics of the subjects (Mean ± SD).

Characteristics	DE	ND
Age	39.41±14.05	37.62±13.17
Sex (male/female)	45/75	30/30
NIBUT-Average (s)	4.70±2.28	8.43±3.31
fBUT-Average (s)	3.69±2.22	4.22±2.20
OSDI Total	30.12±12.91	6.62±3.35
SPEED	12.59±4.63	5.27±2.87
MG grading	22.51±11.68	16.32±9.60
CFS	0.88±0.25	0.35±0.06

Table 2 the relationship between four indicators in DE group

Relationship (r/p)	Value(Mean±SD)	ST1	2-minute ST	rear 3- minute ST	rear 4- minute ST
Value(Mean±SD)		10.93±6.30	5.36±4.63	5.57±2.11	7.21±4.13
ST1	10.93±6.30	1.00	0.796*/<0.001	0.676*/<0.001	0.845*/<0.001
2-minute ST	5.36±4.63	0.796*/<0.001	1.00	0.256*/<0.001	0.508*/<0.001
rear 3-minute ST	5.57±2.11	0.676*/<0.001	0.256*/0.001	1.00	0.884*/<<0.001
rear 4- minute ST	7.21±4.13	0.845*/<0.001	0.508*/<0.001	0.884*/<0.001	1.00

Table 3 the relationship between indicators of ST and OSDI, SPEED, fBUT, MG grading, and CFS in DE group

Relationship (r/p)	Value(Mean±SD)	ST1	2-minute ST	rear 3- minute ST	rear 4- minute ST
Value(Mean±SD)		10.93±6.30	5.36±4.63	5.57±2.11	7.21±4.13
ST1	10.93±6.30	1.00	0.796*/<0.001	0.676*/<0.001	0.845*/<0.001
2-minute ST	5.36±4.63	0.796*/<0.001	1.00	0.256*/<0.001	0.508*/<0.001
rear 3-minute ST	5.57±2.11	0.676*/<0.001	0.256*/0.001	1.00	0.884*/<<0.001
rear 4- minute ST	7.21±4.13	0.845*/<0.001	0.508*/<0.001	0.884*/<0.001	1.00

Relationship (r/p)	Value(Mean±SD)	ST1	2-minute ST	rear 3- minute ST	rear 4- minute ST
value(Mean±SD)		10.93±6.30	5.36±4.63	5.57±2.11	7.21±4.13
OSDI	30.12±12.91				
r/p		-0.198*/<0.001	-0.137*/0.014	-0.081/0.155	-0.242*/<0.0016
SPEED	12.59±4.63				
r/p		-0.124*/0.037	-0.059/0.317	-0.170*/0.005	-0.183*/0.002
fBUT	3.69±2.22				
r/p		0.108*/0.024	0.040/0.403	0.103*/0.036	0.159*/0.001
MG grading	22.51±11.68				
r/p		-0.153*/<0.001	-0.098*/0.022	-0.151/0.001	-0.162*/<0.001
CFS	0.88±0.25				
r/p		0.091/0.156	0.064/0.326	0.176*/0.006	0.108/0.090

Table 4 the correlation between ST and other examinations in ND group

Relationship (r/p)	Value(Mean±SD)	ST1	2-minute ST	rear 3- minute ST	rear 4- minute ST
value(Mean±SD)		11.84±6.16	8.25±6.80	2.73±2.31	7.36±3.42
OSDI	6.62±3.35				
r/p		-0.284*/0.005	-0.086/0.370	-0.082/0.4	-0.316*/0.002
SPEED	5.27±2.87				
r/p		-0.237*/0.025	-0.174*/0.075	-0.170*/0.090	-0.373*/<0.001
fBUT	4.22±2.20				
r/p		0.195*/0.028	0.108/0.187	0.139/0.095	0.191*/0.029
MG grading	16.32±9.60				
r/p		-0.279*/0.001	-0.194*/0.010	-0.048/0.546	-0.284*/<0.001

Table 5 the relationship between rear 4-minute ST and ST1 with examinations

Relationship (r/p)	Value (Mean±SD)	Severe dry eye		Value (Mean±SD)	Borderline dry eye	
		rear 4-minute ST	ST1		rear 4-minute ST	ST1
Value (Mean±SD)		1.87±0.94	2.96±1.67		4.66±0.80	7.81±1.43
OSDI	30.45±10.46			32.46±10.97		
r/p		-0.278*/0.001	-0.207*/0.014		-0.276*/0.026	-0.274*/0.038
SPEED	12.27±2.45			13.69±3.47		
r/p		-0.289*/<0.001	-0.150*/0.043		-0.257*/0.039	-0.220*/0.048
fBUT	3.14±1.27			4.43±2.07		
r/p		0.196*/0.015	0.145*/0.047		0.242*/0.042	0.223*/0.049
MG grading	24.40±10.83			22.72±10.83		
r/p		-0.179*/0.002	-0.168*/0.038		-0.266*/0.021	-0.207*/0.05

Figures

Figure 1

The values of four indicators of ST in DE group

Figure 2

The speed of value of ST in DE group and ND group

Figure 3

The values of four indicators of ST in ND group