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Published in:
Clinical and Experimental Optometry

DOI:
10.1111/cxo.12941

Publication date:
2020

Document Version
Author accepted manuscript

Citation for published version (Harvard):
Alshammeri, S, Madden, L, Hagan, S & Pearce, EI 2020, 'Strip meniscometry tube: a rapid method for assessing aqueous deficient dry eye', *Clinical and Experimental Optometry*, vol. 103, no. 4, pp. 469-473. https://doi.org/10.1111/cxo.12941

RESEARCH

Strip meniscometry tube (SMTube): A rapid method for assessing aqueous deficient dry eye (ADDE)

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Key Words: Aqueous deficient dry eye; Fluorophotometry; Tear turnover rate; SMTube

There is no conflict of interest.
No funding received.

Background

To investigate the utility of strip meniscometry tube (SMTube) for the quantitative assessment of the tear film, by comparing to measurements of tear turnover rate by the gold standard method, fluorophotometry. Also, to determine the viability of this test as a diagnostic tool for aqueous deficient dry eye (ADDE), to inform appropriate clinical management.

Methods

Thirty two participants (15 ADDE; 17 non-ADDE) were recruited. Tear turnover rate of the right eye of each subject was measured with an automated scanning fluorophotometer. SMTube test was carried out. Tear meniscus height was assessed using a slit lamp and eyepiece graticule.

Results

Significant differences between the ADDE and the non-ADDE group were found for all measures: values were respectively; tear turnover rate 7.9±1.8 vs 19.6±5.9 % min^{-1} ($p < 0.001$), SMTube 3.2±1.1 vs 5.7±2.3 mm ($p = 0.001$) and tear meniscus height 0.18±0.05 vs 0.23±0.04 mm ($p = 0.004$). Moreover, significant correlations were found between all diagnostic tests tear turnover rate & SMTube (rho=0.78, p<0.001), tear turnover rate & tear meniscus height (rho=0.54, p<0.001) and SMTube & tear meniscus height (rho=0.47, p<0.01). Using a ROC curve, SMTube showed a sensitivity of 67% and a specificity of 88 % for the diagnosis of ADDE.

Conclusion

Given its performance, availability, speed and the fact it is relatively cheap, the study shows that the SMTube can be used as an alternative to fluorophotometry to assess tear production. It appears from the results that SMTube is a viable minimally-invasive test for the diagnosis of ADDE.

Dry eye can be classified into two aetiological categories; aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE).[1] There are indicators of ADDE such as, a low Schirmer I test value and a reduced tear meniscus height.[2] Adequate tear production is vital in maintaining the health and integrity of the ocular surface.[3, 4] A reduction in tear production leads to a deficiency of the aqueous layer resulting in dry eye disease.[5] Tear turnover rate is commonly used as a synonym for tear production since it measures tear secretion indirectly and tear drainage directly. The majority of the tear volume drains through the punctum while only a small portion of it evaporates or is absorbed by the cornea and the conjunctiva.[6, 16, 39]

Clinically, fluid-absorbing methods such as the Schirmer and cotton thread test have been used to measure tear production.[7] However, due to their low sensitivity and specificity,[8, 38] more accurate diagnostic techniques have been developed to evaluate tear turnover rate, such as automated scanning fluorophotometry.[7, 9, 10]

Fluorophotometry is considered the gold standard in the measurement of tear turnover rate.[6] It allows the accurate assessment of basal tear production by the optical monitoring of the rate of decay of the fluorescence from the tear film for a period of time after instillation.[9, 11] However, this technique has some practical disadvantages such as time needed, cost, and the requirement for special equipment and expertise.[12] Therefore, the need for a clinically viable method of assessing tear production has been suggested.[9, 13]

There have been several attempts to develop such methods including tear clearance rate and tear function index.[12, 14] Tear function index (Liverpool modification) has been developed as a combined version of these methods. It is a modified Schirmer strip impregnated with 1.3 mg of 0.5% fluorescein and placed in the inferior fornix of the eye for 3 minutes. The wetting strip is then measured in millimeters. Furthermore, the staining intensity of the fluorescein is matched with a calibrated panel of dilutions to estimate tear clearance rate. The tear function index is then obtained by dividing the Schirmer score (wetting length of the strip) by the tear clearance rate. Although this method correlates well with tear turnover rate measured by scanning fluorophotometry,[9] there are still issues, such as inter and intra clinician variability because of the partially subjective nature of this method. Additionally, there are only a limited number of grades used to evaluate the intensity of the fluorescence of the strip when matched with dilution standards to determine the level of tear clearance.[9, 12]

Generally, osmolarity is considered to be the most effective single test in the differentiation between normal and dry eye subjects with a sensitivity and specificity of 69% and 92% respectively, based on meta-analysis of study reports over three decades.[15] Moreover, using osmolarity in combination with tear turnover rate and evaporation has been shown to increase the diagnostic accuracy.[16] Methods that measure tear turnover rate have been found to be the best single clinical discriminator in the subclassification of dry eye e.g. ADDE versus evaporative dry eye with a sensitivity of 86% and specificity of 75%, with a 12%/min cut off value.[16, 17]
The strip meniscometry tube (SMTube) has been proposed as a method for the quantitative assessment of the tear film for more than a decade.[13] The SMTube is a medical device, which uses a single-use sterile strip composed of a fluid-absorbing material.[13] It has been used in some clinical studies. However, its performance has not been fully characterized.[13, 18]
The aim of this study is to determine the utility of the SMTube to assess tear production, by comparing to measurements of tear turnover rate by a gold standard method, fluorophotometry. This will determine if this new test can be adopted to allow the diagnosis of ADDE in a clinical setting.

METHODS

Thirty-two participants (15 ADDE; mean age 54±17 (SD) years, 10F; 5M) and (17 non-ADDE; mean age 32±3 (SD) years, 8F; 9M) were recruited to the study. The study was conducted according to the principles contained in the Declaration of Helsinki. Ethical approval was obtained from the School of Health and Life Sciences Ethics Committee at Glasgow Caledonian University. Written informed consent was given by all subjects prior to participation.
Two groups of subjects were enrolled into this study: TTR was measured in all subjects. The subjects were then classified into two groups: Non-ADDE group; tear turnover rate > 10 % min^{-1}. ADDE group, turnover rate ≤ 10 % min^{-1}.[31, 35] Their status of EDE was not determined in either group.
To ensure near equal numbers in each group, pre-screening was used to recruit sufficient ADDE subjects. Pre-screening included reported symptoms (McMonnies questionnaire <14.5 score),[19] tear break-up time, using Keeler Tear Scope, non-invasive tear breakup time of < 10 seconds and a Schirmer of ≤ 10 mm in 5 minutes.

The exclusion criteria were signs of blepharitis by clinical examination, previous diagnosis of Sjögren's syndrome or recent ocular surgery.

Each respondent of both groups was asked to attend for one visit that lasted approximately 30 minutes. All tests were applied during the period 12-2 p.m and were done in the same order. The tear turnover rate of the right eye of each subject was measured with an automated scanning fluorophotometer (Fluorotron Master). The SMTube was then applied after two minutes to the lower tear meniscus of the same eye. After 5 seconds, the length of the stained portion was measured. After five minutes, tear meniscus height was then measured using a slit lamp and eyepiece graticule. The analysis of the Fluorotron data was not carried out until some time after data collection. This minimized any observer bias that might occur if tear turnover rate was known prior to measuring the other parameters.

Fluorophotometry

Tear turnover rate was measured using an automated scanning fluorophotometer (Fluorotron Master; Coherent Radiation, Inc., CA, USA) using the standard excitation and emission filters. Without touching the ocular surface or lid, and by using an air displacement micropipette (Gilson Inc., WI, USA) to ensure minimal reflex lacrimation, 1 µl of 2% sodium fluorescein (Bausch & Lomb UK Ltd., Kingston-Upon-Thames, UK) was instilled into the lower temporal conjunctival sac. Further, TTR relies on taking measurements four minutes after instillation to avoid any possible effect of reflex lacrimation. The rate of decay of fluorescence from the tear film was then calculated by plotting the log decay.[6]

SMTube and tear meniscus height

The SMTube (Echo Electricity Co., Ltd.Tokyo, Japan) was applied to the lateral lower lid tear meniscus of the right eye. The strip absorbs tears by capillary action of the center of the strip. A blue dye (the indicator) placed at the tip of the strip is then dissolved in the absorbed tears. After five seconds, the length of the stained tear column was measured and recorded in millimetres (Figure 1).[13, 18]

In this study tear meniscus height was measured using a slit lamp biomicroscope (Haag-Streit AG, Slit Lamp 900 BM, Koeniz, Switzerland) with a calibrated graticule scale in the ocular eyepiece.[21]

Statistical Analysis

Data was analysed using SPSS (IBM Corp. IBM SPSS Statistics for Windows, Version 23.0. IBM Corp. Armonk, NY) and found not to follow a normal distribution. Non-parametric methods were therefore used throughout. ROC curve technique was used to determine a diagnostic cut-off value. Sensitivity and specificity, based on both non-ADDE and ADDE groups, for each test were calculated for the ability to discriminate between groups.

RESULTS

Tear Production

Subjects with ADDE had significantly lower values for all tests, which indicated reduced tear production (Table 1). ($p < 0.05$ Mann-Whitney U test).

As expected, a significant difference was found in tear turnover rate between ADDE and non-ADDE groups. This was in part due to the inclusion criteria employed. A similar pattern was seen for SMTube results. The results also showed a significant difference in tear meniscus height between ADDE and non-ADDE subjects.

Correlations

The Spearman's rank correlation coefficients between tear turnover rate, SMTube and tear meniscus height were calculated (Figure 2). Both parameters showed significant correlations with the laboratory based tear turnover rate. The most interesting relationship was between tear turnover rate and the SMTube and shows these tests are highly correlated (rho = 0.78, $p < 0.001$) indicating that the SMTube could be used as a surrogate for fluorophotometry to assess tear production.

ROC Curve Analysis

To evaluate individual tests and to determine cut-offs in the differentiation of ADDE from non-ADDE, a ROC curve technique was used for both SMtube and tear meniscus height (Table 2). A cut-off of 3.75 mm at 95% confidence interval for SMTube gave an area under the ROC curve of 0.83 and a sensitivity of 63% and a specificity of 88% in discriminating ADDE (Figure 3). SMTube had a higher specificity (88%), while tear meniscus height had a higher sensitivity (86%), however higher specificity is favourable in this case since the test is used to identify a non-serious condition (e.g. dry eye disease) where we want to avoid false positive diagnosis when possible.

DISCUSSION

The International Dry Eye Workshop (TFOS DEWS II diagnostic criteria) states that a suspected dry eye case can be diagnosed through a structured patient history,[22-24] fluorescein-aided assessment of tear film break-up time,[25] ocular surface staining with fluorescein/lissamine green,[26, 27] Schirmer test with or without anesthesia[28] and finally inspection of meibomian gland orifices and the surrounding lid margin with expression of meibomian secretion.[26]

The aetiologies of dry eye can be difficult to diagnose in the early stages.[1, 29] As a result of that, it is important for clinicians to have available methods to diagnose and differentiate between dry eye sub-types[1]. There are some indicators to differentiate between the main two forms of dry eye such as low Schirmer I test value, despite lack of standardisation of this test,[28] and a reduced tear meniscus in ADDE.[2] In evaporative dry eye, lid margin pathology is apparent such as obstructed meibomian gland orifices and thickened meibomian gland secretion. However, most cases of dry eye (80%) are likely to be a combination of the two forms showing increased tear film osmolarity and ocular surface damage.[30] Therefore, ADDE & evaporative dry eye are difficult to differentially diagnose.[1, 30]

Tear turnover rate measured by an automated scanning fluorophotometry is considered the best available method in detecting ADDE.[17, 31, 32] However, this method is not available in a clinical setting due to time taken and specialist equipment required. In this study, SMTube was evaluated in order to assess its correlation with other tear production tests and assess the efficacy of this test in detecting ADDE.

The current study had an objective of examining the performance of SMTube compared to fluorophotometry, the gold standard. Previous reports have shown correlations between SMTube and other tear production assessment methods such as tear meniscus height measurements and the Schirmer test.[13, 18, 34] Unfortunately, the tests assessed in these previous studies have limitations such as invasive nature that can cause reflex tearing for the Schirmer test,[9, 28] or poor inter-observer and intra-observer repeatability and a lack of standardization of tear meniscus height measurement using optical coherence tomography.[26, 33] On the other hand, the rapid nature of these tests allowed a large study population.[13, 18] However, fluorophotometry, which was used in this study, is a time consuming laboratory measure, which imposed limitations on the study size but did offer access to the best method of measuring tear production.

Both parameters, SMTube and tear meniscus height, showed significant correlations with the laboratory-based tear turnover rate measurement, which suggests that these clinical tests may be candidate surrogates for tear turnover rate. The stronger relationship between tear turnover rate and SMTube (Figure 2) indicates that SMTube is the most viable alternative to fluorophotometry in the assessment of tear production.

The SMTube also showed a high specificity in ADDE diagnosis, which will ensure that healthy people will not be treated unnecessarily. However, it could be expected to have higher sensitivity when combined in parallel with other diagnostic tests such as TBUT. Previous reports of SMTube with a cutoff value of ≤ 4 mm found sensitivity and specificity to be 84% and 58% respectively.[24] However, it should be noted that this referred to the detection of dry eye rather than ADDE. The current study is the first to look at the SMTube diagnostic ability in this group. Applying the cutoff value from these previous reports to our study would increase sensitivity from 67% to 87%. However, specificity would decrease dramatically from 88% to 59%.

The benefit of having a viable test in the diagnosis of ADDE will help reduce complications in dry eye management. For example, using punctual plugs for dry eye patients with normal tear production can cause epiphora.[36]

The interpretation of the results of this study may exhibit some limitations, as the ADDE populations were intentionally defined to achieve an unambiguous classification. In this respect, the findings can be considered to reflect the diagnostic capacity of the SMTube technique to distinguish between non ADDE subjects from those with ADDE, which may not take into account consideration of borderline dry eye. In future studies a cross section of normal, evaporative dry eye and ADDE subjects will be studied to assess the diagnostic accuracy and repeatability of SMtube in a general population.

CONCLUSION

In conclusion, the study shows that the SMTube in addition to its advantages of cost, speed, and availability, can be used as a surrogate of tear turnover rate measurement by fluorophotometry. From the results of this study, we advocate that SMTube should be adopted as a test to detect ADDE.

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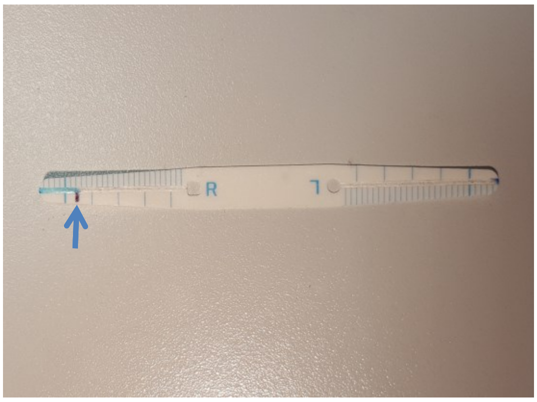
Table 1. Median and Interquartile Range (IR) of tear production assessments in this study (tear turnover rate (TTR), SMTube and tear meniscus time (TMH)) for subjects with ADDE and non-ADDE subjects.

	ADDE (Median/IR)	non-ADDE (Median/IR)
TTR $p < 0.001$*	7.8 (2.3) % min^{-1}	19.4 (9.1) % min^{-1}
SMTube p=0.001*	3.3 (1.5) mm	5.0 (3.6) mm
TMH p=0.004*	0.20 (0.09) mm	0.25 (0.05) mm

(* = Significant difference found between ADDE and non–ADDE groups)

Table 2: The performance of SMTube and TMH in the discrimination of ADDE and non-ADDE subjects.

Test	Cut-off	Sensitivity	Specificity
SMTube (mm)	3.75	67%	88%
TMH (mm)	0.23	86%	63%



A

B

Figure 1. (A) A single SMTube strip with the ability to measure from both eyes (R, L); length of the stained tear column arrow in the central channel, gives the SMtube value in millimetres. (B) SMTube being applied to the lateral lower lid tear meniscus without touching the ocular surface.

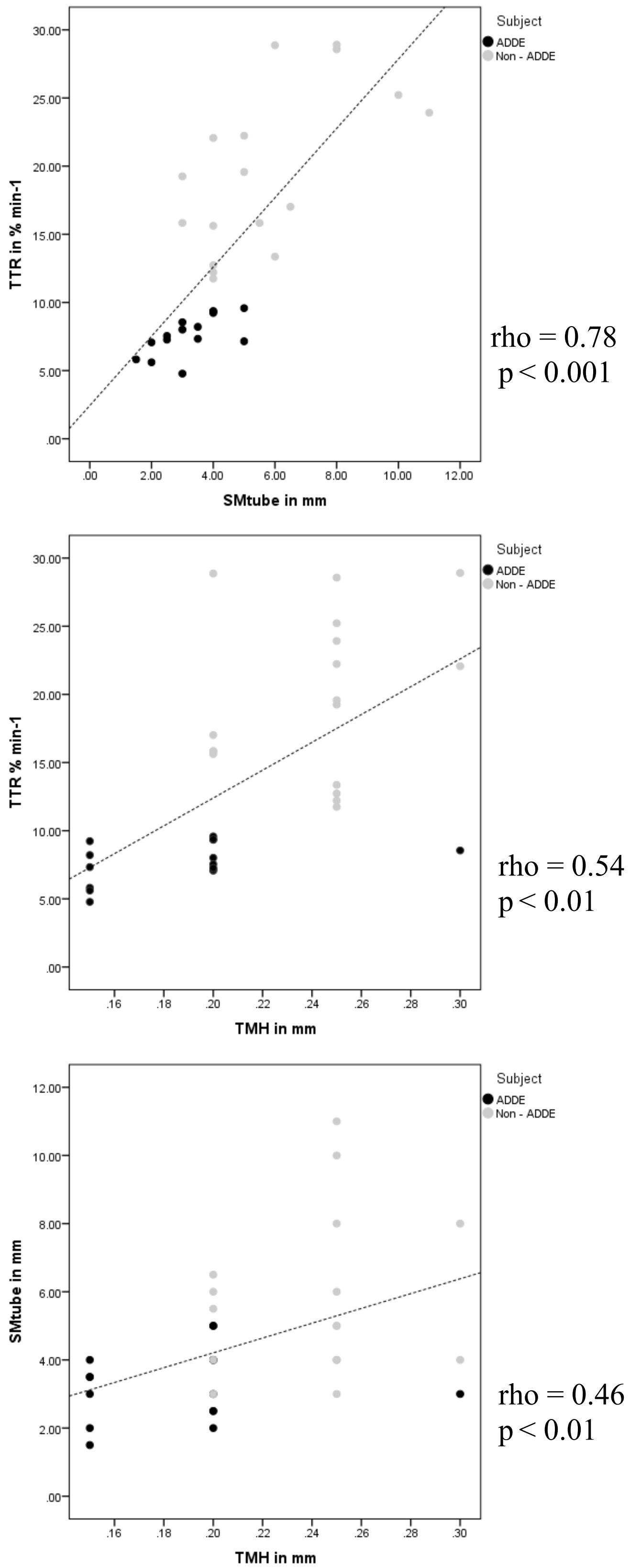


Figure 2. Scatter plot of relationships between TTR, SMTube and TMH for ADDE (dark spots) and non-ADDE subjects (light spots). Correlation was derived from the combined data of ADDE and non ADDE subjects. Spearman's correlation, rho and p values are shown on each plot. SMTube showed the strongest correlation (rho=0.78 p <

0.001) with the laboratory-based TTR. Rho is analogous to R obtained in the Pearson correlation where a perfect positive relationship would give a value of 1.

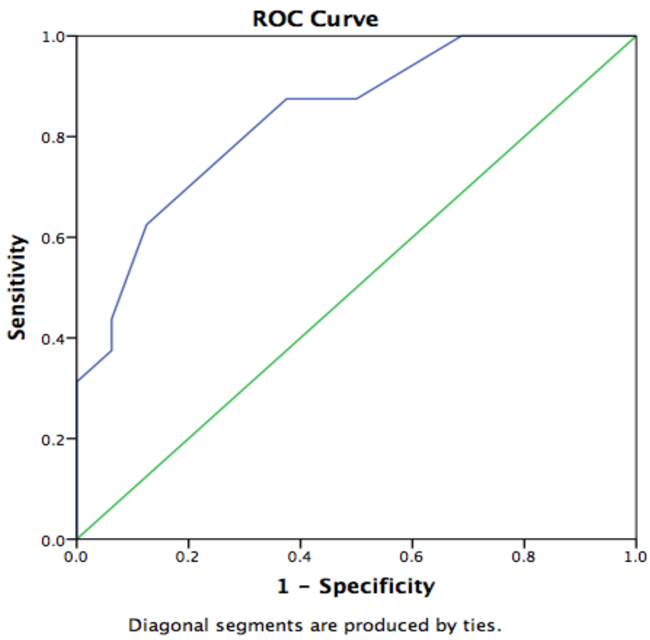


Figure 3. ROC curve of SMTube with a cutoff value of 3.75 mm in the diagnosis of ADDE, the test shows a sensitivity of 67% and a specificity of 88%.