Coll. Antropol. **35** (2011) 4: 1105–1113
Original scientific paper

Differential Diagnostic Performance of Rose Bengal Score Test in Sjøgren's Syndrome Patients

Igor Knezović[1], Ivan Alajbeg[2], Dalibor Karlović[3], Josip Pavan[1], Nada Vrkić[4] and Ana Bišćan[1]

[1] University of Zagreb, Dubrava University Hospital, Department of Ophthalmology, Zagreb, Croatia
[2] University of Zagreb, School of Dental Medicine, Department of Oral Medicine, Zagreb, Croatia
[3] University of Zagreb, »Sestre Milosrdnice« University Hospital Center, Department of Psychiatry, Zagreb, Croatia
[4] University of Zagreb, »Sestre Milosrdnice« University Hospital Center, Department of Chemistry, Zagreb, Croatia

ABSTRACT

Aim of the study was to evaluate the diagnostic performance of the Rose Bengal score test for Sjøgren's syndrome (SS), and to explore differences between other tests and examinations. All participants were examined, including (but not limited to) unstimulated (UWS) and stimulated (SWS) whole saliva, labial gland biopsy (LGB or focus score), ophthalmologic questionnaire (ocular surface disease index OSDI) and objective tests: Schirmer test 1 (Sch.1), Schirmer test 2 (Sch.2), Tear Break-up Time (TBUT) test and Rose Bengal score (RBS). Data were analyzed using Mann Whitney U-test, Receiver Operating Characteristic analysis, with specificity and sensitivity calculations and Spearman's correlation test. ROC curves showed a poor diagnostic performance of TBUT and OSDI. Sch.1, Sch.2 and LGB all exhibited a high diagnostic performance. RBS exhibited the best performance (sensitivity 100,00; specificity 100,00; AUC 1,000). Study reveals the scarce reliability of TBUT, OSDI and Sch.1, and emphasizes RBS as the test of choice in the SS diagnosis.

Key words: *Rose Bengal, Sjøgren's syndrome, Keratokonjunctivitis Sicca, Xerostomia, salivary gland diseases, Tear Break-Up Time test, ophthalmologic questionnaire, labial gland biopsy*

Introduction

Sjøgren's syndrome (SS) is an autoimmune exocrinopathy of unknown etiology, prominently affecting the salivary and lacrimal glands[1]. Xerostomia and xerophthalmia are often the presenting symptoms of the disease.

It is characterized by progressive lymphocytic infiltration of exocrine glands and epithelia in multiple sites[2–4]. The peak incidence is in the fourth and fifth decades of life, with a female to male incidence ratio of 9:1. The major diagnostic tool is the labial salivary gland biopsy, which characteristically shows focal lymphocytic infiltration[5]. It is also a painful procedure with small but significant proportion of unreliable results[6].

Systematic multidisciplinary approach is required in proper evaluation of SS, including assessment of the oral, ocular and systemic components of the disease. Numerous criteria have been proposed to facilitate the diagnosis of SS. The American-European Consensus Group criteria[4] proved to be the most practical, since they take into consideration the multisystemic nature of the disease. The set of criteria includes 6 different items and 4 of them must be present in patients for the diagnosis of SS.

Two typical items are included in the majority of the diagnostic sets, subjective symptoms and tests for eye dryness, but little agreement on the cut off values is present. The ocular surface is now considered as an integrated unit[7], and any dysfunction results in a scarce or unstable preocular tear film and in the presence of unrefreshed tears in which soluble mediators store up. A range of criteria have been proposed for the evaluation of patients with dry eye. The most frequently used tests are Schirmer test 1 and Tear Break-up Time test[8].

Regardless of the fact that many scientific evidence suggest to also include other tests in the assessment of dry eye[9], in the practice it is still based upon a low Sch.1 and/or TBUT. The purpose of the present work was to determine the diagnostic performance of Rose Bengal score (RBS) test in differential diagnosis of SS *vs.* other non-Sjøgren's »Sicca syndrome«.

Received for publication February 19, 2010

Materials and Methods

The study included 66 patients, examined during the period April 2006–May 2008 and grouped as follows:

- Sjøgren's syndrome (SS) patients (48 subjects), diagnosed according to the American-European Consensus Group criteria[4];
- Sicca syndrome (Sicca S) patients (18 subjects) reporting subjective symptoms of xerophthalmia and xerostomia, but who did not satisfy the classification criteria for SS.

Group and sex distribution data are reported in Table 1.

TABLE 1
NUMBER AND SEX DISTRIBUTION OF PATIENTS IN GROUPS WITH SJØGREN'S SYNDROME (SS) AND SICCA SYNDROME (SICCA S)

TOTAL PATIENTS NUMBER (N=66)		
	Male (N=6)	Female (N=60)
SS (N=48)	6	42
Sicca S (N=18)	0	18
Total (N=66)	6	60

Patients were asked to answer on 12 questions from a validated questionnaire (ocular surface disease index OSDI). Questions were associated to their subjective symptoms felt the week before. The score of the questionnaire ranges from 0 to 12 (no disability), to 13–22 (light dry eye), to 23–32 (moderate dry eye), to 33–100 (severe dry eye)[10].

The Schirmer test were performed as described elsewhere[9] by using sterile Schirmer strips without anesthesia (Sch.1) or after application of tetracaine 0.5% (Sch.2), in room controlled for lighting (dim light room), temperature (20–22°C), and humidity (40–60%). Abnormal value was regarded as ≤10 mm/wetting after 5 min for Sch.1 and ≤5 mm/wetting after 5 min for Sch.2.

The TBUT was performed as described elsewhere[9] and the time of rupture <10 s was considered as abnormal.

Rose Bengal staining was performed as already reported and scored[11]. Pathological vital staining was scored as >9/18 in six areas measured.

Statistical analysis

Data were statistically evaluated by applying the Statistical Package for the Social Sciences (SPSS) for Windows 11.0 for the independent sample t-test, the Mann-Whitney U-test for unpaired data, and the logistic regression for selected groups of tests. For nonparametric data the descriptive statistic applied were the analysis of median and 25–75 percentiles. P values less than 0.05 were regarded as statistically significant.

The prevalence of the SS (the proportion of patients who have the disease in the population under testing) was calculated using the population included in our study as a reference. Each of the test performed were analysed for sensitivity (the percentage of symptomatic patients who tested positive, a large sensitivity means that a negative test can rule out the disease) and specificity (the percentage of normal subjects who tested negative, a large specificity means that a positive test can confirm the disease)[12]. Specificity and sensitivity were calculated comparing SS patients *vs.* Sicca S patients. Data were also processed in order to calculate receiver-operating characteristics (ROC) curves[13]. ROC curve expresses the diagnostic exactness of test variables by plotting the sensitivity of the test against the specificity at all possible thresholds.

We used the likelihood ratio, a measure that combines information about the sensitivity and specificity, and offers a direct valuation of how much a positive or negative result changes the likelihood that a patient would have the disease, to summarize the data about diagnostic tests. The likelihood ratio for positive results (LR+; sensitivity divided by 1-specificity) demonstrates how much the odds of the disease increase when a test is positive.

Results

Table 2 summarizes the medium±SD of the values resulted from the study, collected from each group of patients. Data shown in separate figures represents min-max values range (bounded with lines), results values from 25% to 75% and median (black line) from each group of patients.

Unstimulated whole saliva (UWS) is expressed in mL/5 min. Mean values in SS patients were 0.33±0.42

TABLE 2
SUMMARY OF THE RESULTS ($\bar{X}$±SD) IN GROUP WITH SJØGREN'S SYNDROME (SS) AND SICCA SYNDROME (SICCA S) FOR EACH PROVIDED TEST

Test	Measure	SS	Sicca S	p
Unstimulated whole saliva (UWS)	mL/5min	0.33±0.42	0.65±0.21	<0.001
Stimulated whole saliva (SWS)	mL/5 min	0.88±1.10	1.90±0.47	<0.001
Ocular surface disease index (OSDI)	Score	52.66±22.02	34.75±11.77	<0.003
Schirmer test 1 (Sch.1)	mm/5 min	13.81±14.30	29.17±12.70	<0.001
Schirmer test 2 (Sch.2)	mm/5 min	4.72±5.66	17.17±11.06	<0.001
Tear Break-up Time (TBUT) test	Seconds	8.69±6.39	13.00±6.36	<0.008
Rose Bengal score (RBS)	Score	10.56±3.35	2.83±2.33	<0.001

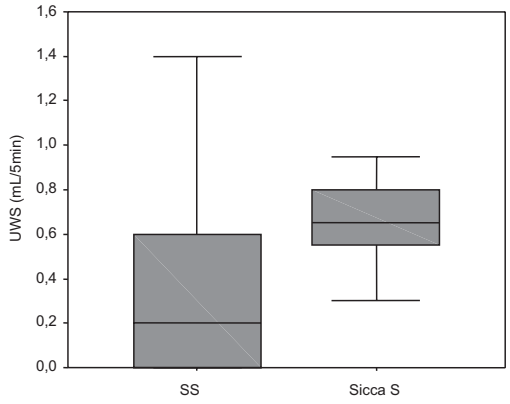

Fig. 1. Median (black line), results from 25%–75% and range min-max (bounded with lines) values for unstimulated whole saliva (UWS) in groups of patients with Sjøgren's syndrome (SS) and sicca syndrome (Sicca S).

mL/5 min and in Sicca S patients were 0.65±0.21 mL/5 min, with statistically significant differences ($p<0.001$) between groups (Table 2).

Median value, results from 25%–75% and min-max values range for UWS are presented in Figure 1.

Stimulated whole saliva (SWS) is expressed in mL/5 min. Medium values in SS patients were 0.88±1.10 mL/5 min and in Sicca S patients were 1.90±0.47 mL/5 min, with statistically significant differences ($p<0.001$) between groups (Table 2).

Median value, results from 25%–75% and min-max values range for SWS are presented in Figure 2.

Dry eye symptoms were reported by all patients (score of the subjective symptom questionnaire always >12), ranging from moderate in Sicca S to severe in SS patients, with statistically significant differences ($p<0.003$) between groups (Table 2).

Median value, results from 25%–75% and min-max range values for OSDI are presented in Figure 3.

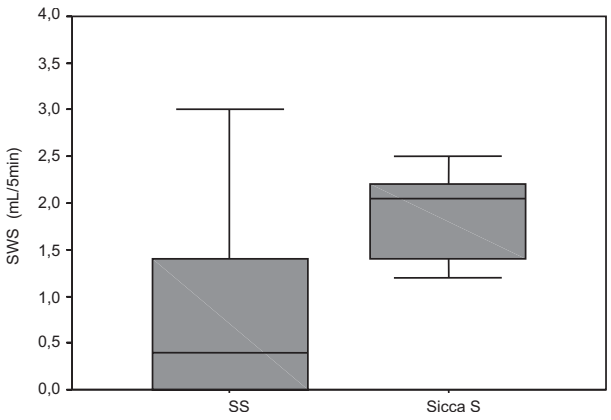

Fig. 2. Median (black line), results from 25%–75% and range min-max (bounded with lines) values for stimulated whole saliva (SWS) in groups of patients with Sjøgren's syndrome (SS) and sicca syndrome (Sicca S).

Mean values of pathological Schirmer test 1 (paper wetting <10 mm/5 min) were not found in any group, but with statistically significant differences ($p<0.001$) between groups (Table 2).

Median value, results from 25%–75% and min-max values range for Schirmer test 1 are presented in Figure 4.

Mean values of Schirmer test 2 showed a pathological decrease of tear production only in SS patients, with statistically significant differences ($p<0.001$) between groups (Table 2).

Median value, results from 25%–75% and min-max values range for Schirmer test 2 are presented in Figure 5.

Tear Break-up Time (TBUT) test showed pathological mean values in SS group, with statistically significant differences ($p<0.008$) between groups (Table 2). Median value, results from 25%–75% and min-max values range for TBUT are presented in Figure 6.

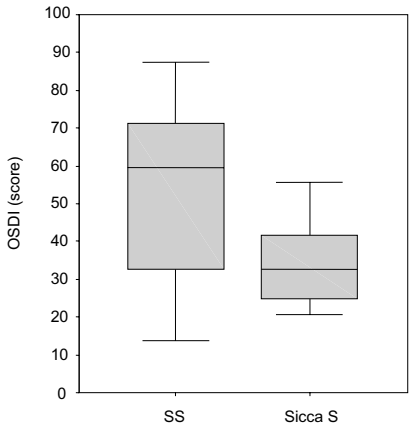

Fig. 3. Median (black line), results from 25%–75% and range min-max (bounded with lines) values for Ocular surface disease index (OSDI) in groups of patients with Sjøgren's syndrome (SS) and sicca syndrome (Sicca S).

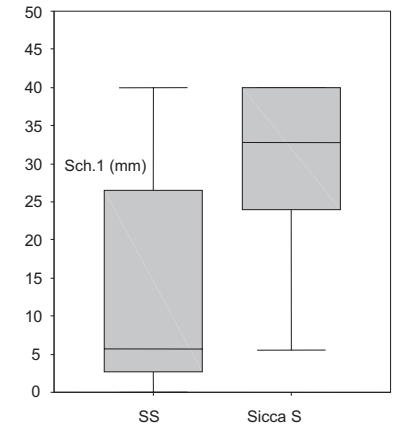

Fig. 4. Median (black line), results from 25%–75% and range min-max (bounded with lines) values for Schirmer test 1 (Sch.1) in groups of patients with Sjøgren's syndrome (SS) and sicca syndrome (Sicca S).

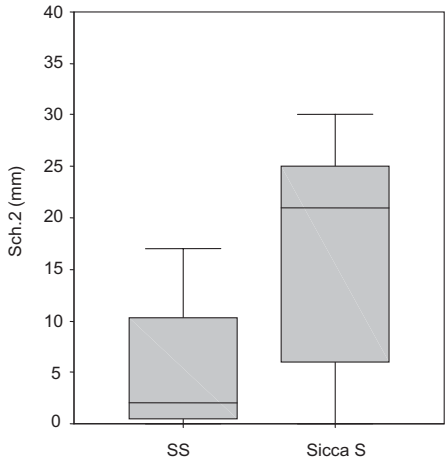

Fig. 5. Median (black line), results from 25%–75% and range min--max (bounded with lines) values for Schirmer test 2 (Sch.2) in groups with Sjøgren's syndrome (SS) and sicca syndrome (Sicca S).

The Rose Bengal score resulted in the pathological range only in the SS patients, with statistically significant differences ($p<0.001$) when compared to Sicca S group (Table 2).

Median value, results from 25%–75% and range min--max values for RBS are presented in Figure 7.

In our study, the Schirmer test 1 performed poorly as a diagnostic test for SS patients (sensitivity 75.00, specificity 83.33) and ROC plot analysis (Figure 8) demonstrates relatively flat curve, close to diagonal line (area under the curve 0.781).

Schirmer test 2 showed higher sensitivity (100.00) and slightly worse specificity value (66.67) in comparison with Schirmer test 1 (Table 3), with area under the curve 0.802 (Figure 9).

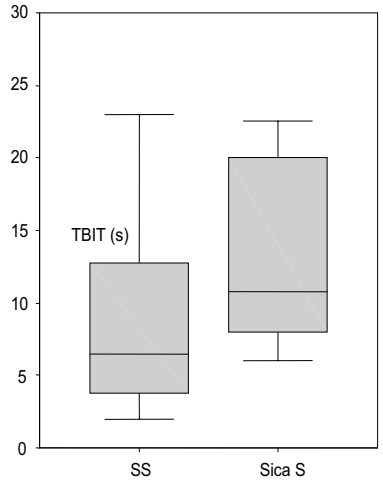

Fig. 6. Median (black line), results from 25%–75% and range min--max (bounded with lines) values for Tear Break-up Time (TBUT) test in groups of patients with Sjøgren's syndrome (SS) and sicca syndrome (Sicca S).

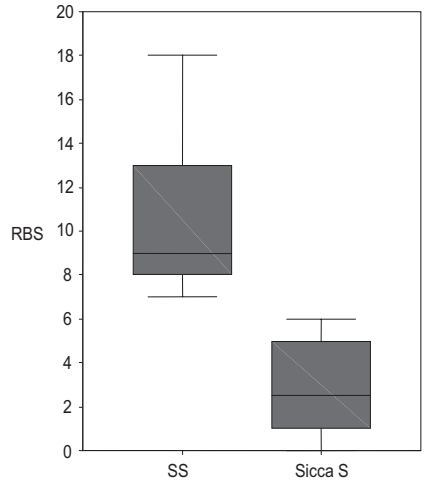

Fig. 7. Median (black line), results from 25%–75% and range min--max (bounded with lines) values for Rose Bengal score (RBS) in groups of patients with Sjøgren's syndrome (SS) and sicca syndrome (Sicca S).

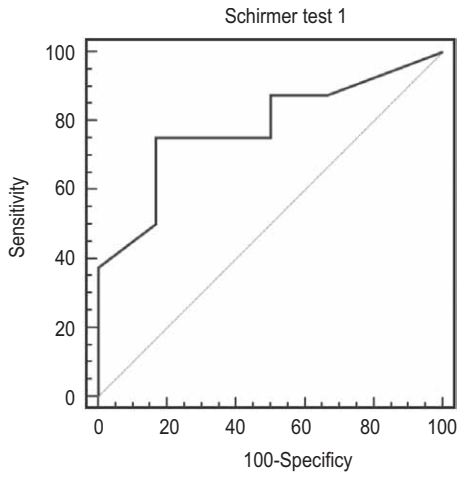

Fig. 8. Receiver Operating Characteristic (ROC) curve for Schirmer test 1.

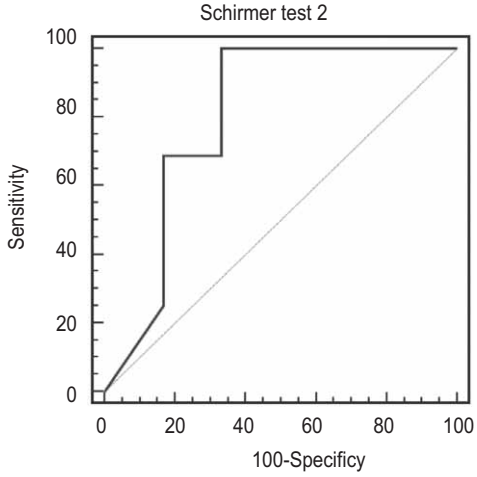

Fig. 9. Receiver Operating Characteristic (ROC) curve for Schirmer test 2.

TABLE 3
CUT OFF VALUES AND COORDINATES OF RECEIVER OPERATING CHARACTERISTIC CURVES WITH LIKELIHOOD RATIO (LR) FOR POSITIVE (+) AND NEGATIVE (–) RESULTS FOR EACH PROVIDED TEST

Test	Cut off	Sensitivity	Specificity	+LR	–LR
OSDI	>55.6	56.25	100.00	0.00	0.44
Sch.1	≤23	75.00	83.33	4.50	0.30
Sch.2	≤17	100.00	66.67	3.00	0.00
TBUT	≤7.5	62.50	83.33	3.75	0.45
Rose Bengal score	>6	100.00	100.00	0.00	0.00
Focus score	≤1	56.25	100.00	0.00	0.44

TABLE 4
STATISTICAL VALUES REPORT WITH AREA UNDER THE CURVE, STANDARD ERROR AND 95% CONFIDENCE INTERVAL FOR EACH PROVIDED TEST

Test	Area under the curve	Standard error	95% confidence interval
OSDI	0.740	0.0632	0.617–0.840
Sch.1	0.781	0.0698	0.662–0.874
Sch.2	0.802	0.0674	0.686–0.890
TBUT	0.714	0.0759	0.589–0.818
Rose Bengal score	1.000	0.000	0.945–1.000
Focus score	0.823	0.0646	0.709–0.906

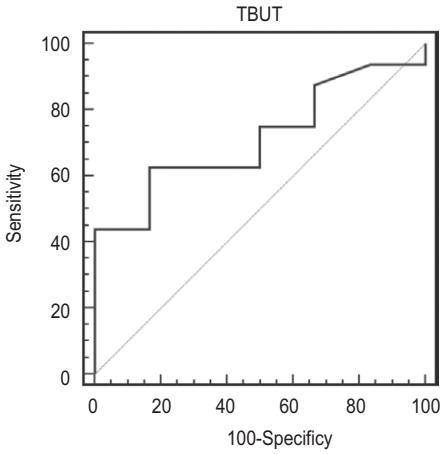

Fig. 10. Receiver Operating Characteristic (ROC) curve for Tear Break-up Time (TBUT) test.

The TBUT also performed poorly as a diagnostic test for SS with sensitivity 62.50 and specificity 83.33 (Table 3). ROC plot analysis also indicated rather low accuracy of the test (area under the curve 0.714) (Figure 10).

The OSDI performed somewhat better than TBUT, with sensitivity 56.25 and specificity 100.00 (Table 3). ROC plot analyses demonstrated a curve slightly approaching the upper left corner of the diagram (Figure 11), displaying somewhat larger area under the curve (0.740), (Table 4).

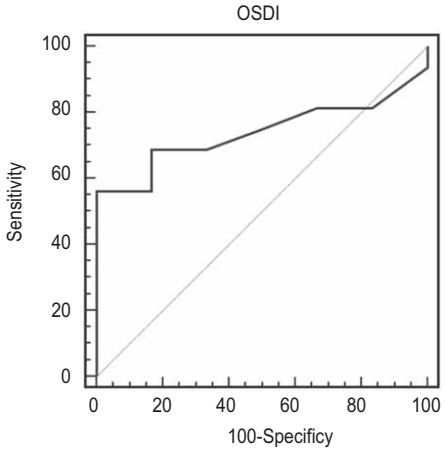

Fig. 11. Receiver Operating Characteristic (ROC) curve for Ocular surface disease index (OSDI).

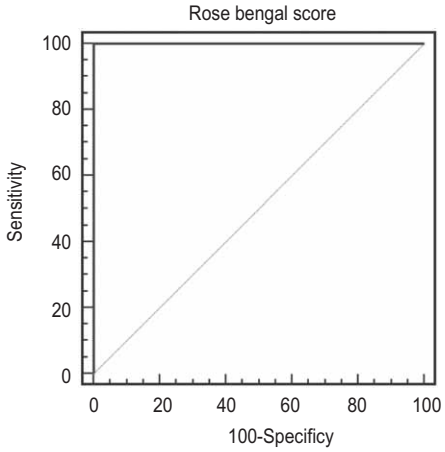

Fig. 12. Receiver Operating Characteristic (ROC) curve for Rose Bengal score (RBS).

In the present study, the tests that showed the best performance were Rose Bengal score with sensitivity 100.00 and specificity 100.00 (Table 3), area under the

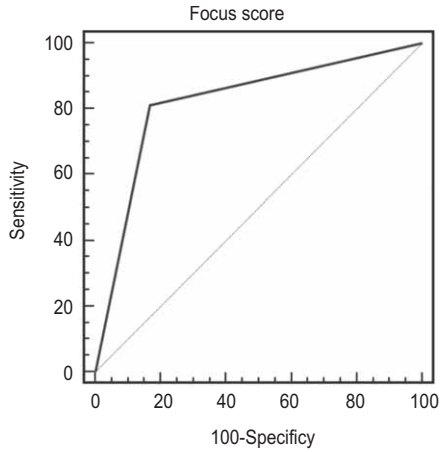

Fig. 13. Receiver Operating Characteristic (ROC) curve for focus score.

curve in the ROC plot analyses being 1.000 (Table 4, Figure 12); and labial gland biopsy focus score with sensitivity 56.25 and specificity 100.00 (Table 3), area under the curve in the ROC plot analysis being 0.823 (Table 4, Figure 13). The ROC curves of these tests showed the tendency to approach the upper left corner of the diagram, especially the curve related to Rose Bengal score, indicating the highest diagnostic performance.

Discussion

Dry eyes and dry mouth usually occur in patients suffering from a variety of autoimmune diseases, especially in Sjøgren's syndrome (SS). Sjøgren's syndrome causes substantial discomfort in mouth[14,15]. Several recent studies evaluated xerostomia-relieving effects of salivary gland stimulation by low level laser therapy[16], by systemic pilocarpine[17,18], as well as by intraoral electrostimulation device[19]. These modalities have increased salivary output in published trials. However, pilocarpine shows systemic side effects, whereas intraoral electrostimulation device and low level laser are costly and not universally available.

Xerophthalmia occurring in SS causes ocular morbidity and is a marker of disease progression. The ocular surface status is included in most diagnostic algorithms, either in the form of questionnaires and objective tests, such as Schirmer test 1 and Schirmer test 2, TBUT and surface staining with vital dye – Rose Bengal score (RBS)[12].

Despite the importance of proper use of diagnostic tests in clinical decisions, many tests have not yet been subjected to precise evaluation to determine their clinical utility.

There is much debate about the usefulness and exactness of the Sch.1. Vitali and associates, back in 1994, demonstrated that it is a reliable test for the diagnosis of SS[11], while other authors discussed its role[20,21], showing that Sch.1 has a moderate repeatability from visit to visit and displays a weak correlation with subjective symptoms of dryness[22]. The most widely recognized opinion is that Sch.1 has no significant diagnostic value in mild to moderate dry eyes and only a very low Sch.1 score can be regarded as a good indicator of an aqueous deficiency.

Cut off values for Sch.1 is wetting ≤5 mm/5 min in the American-European Consensus Group criteria for SS[4]. In our study, cut off value is far above that reference, exactly ≤23 mm (sensitivity 75.00 and specificity 83.33). This relatively high cut off is indicator of low sensitivity at lower values. That kind of test cannot present clear distinction between these two groups of patients.

If we use a common baseline test, the sensitivity would fall to approximately 65.00; while the specificity would have remained unchanged. Such an interpretation of the text would significantly diminish its clinical importance and an area under the ROC curve, which was 0.781 in our study. The standard error was 0.0698 with 95% confidence interval of 0.662–0.874 (Table 4).

According to the American-European Consensus Group criteria, objective ocular signs are positive if any of ophthalmic tests (Sch.1 or RBS) showed pathological values[4]. It is understandable that a large number of patients in our and in other studies, are only to be diagnosed with SS based on the results of RBS's, when it comes to that classification category. Sch.1 than gets the relative importance of a single test, including the impact of disease stage and therapy on the measurement results. However, the diagnostic value of Sch.1 is not negligible, since the difference between the group of patients with SS and Sicca S is statistically significant ($p<0.000$, Mann Whitney $U=189.00$). Mean values of the test in subjects with SS amounted to 13.81 mm, and in subjects with Sicca S 29.17 mm.

It can be concluded that in the differential diagnosis of SS, Sch.1 often gives false negative results, if we take the limit value of accepted 5–15 mm/min. In our, as well as other similar surveys, more than half of the patients had negative values for Sch.1[12,20] and if the marginal test value does not increase, its differential diagnostic value will remain relatively weak.

Version of Schirmer test used in this study was with a local anaesthetic application (Schirmer test 2 (Sch.2)), in order to avoid external stimulus and show basal secretion. Sch.2 showed a high sensitivity and satisfactory specificity and, as such, a good analyticity in the differential diagnosis of a SS. Differences among the results were statistically significant between patients with SS and Sicca S ($p<0.001$, Table 2, Mann Whitney $U=171.00$), suggesting the importance of simultaneous performance of both Schirmer tests. Mean test values in group of subjects with SS amounted 4.72 mm, and in the group with Sicca S 17.17 mm. Similar to Sch.1, common marginal values for this test are not in accordance with values obtained in our study. According to current criteria, strip wetting marginal value for the Sch.2 is ≤5 mm/5 min[12], whereas in our study this value reached ≤17 mm. With such a value, the sensitivity of the test was 100.00 and the specificity 66.67. If we apply the usual ≤5 mm, then the sensitivity would have fallen to 68.75, with equal specificity value, which would significantly reduce the clinical test analyticity. Also, the area under the ROC curve at Sch.2 is greater than at Sch.1 (0.802:0.781), which makes it more usable and sensitive in the differential diagnosis of SS. The standard error was 0.0674, with 95% confidence interval of 0.686–0.890. However, it is important to note that there is no statistically significant difference between ROC curves of these two tests ($p<0.606$).

Differences found in unstimulated whole saliva (UWS) between patients with SS and Sicca S were statistically significant ($p<0.001$, Mann Whitney $U=198.00$), with mean values for SS of 0.33 mL/5 min, and for the Sicca S of 0.65 mL/5 min. Likewise, the differences in obtained values of stimulated whole saliva (SWS) among subjects with SS and Sicca S were significant ($p<0.001$, Mann Whitney $U=148.50$, mean value of SS 0.88 mL/5 min, the mean value of Sicca S 1.90 mL/5 min). From these results it is evident that the investigated population had both

hyposecretion components (lacrimal and salivary), and that the differences among the groups in both cases are significant. Such finding was also expected and it might be assumed that the lacrimal gland biopsy would provide histological findings (positive focus score) similar to biopsy of labial salivary glands (LGB). This assumption is based on parallel functional deficit of both exocrine glands as well on some other similar studies[23,24], which often favor the lacrimal gland biopsy over LGB.

Data from our study demonstrated that a negative TBUT cannot exclude diagnosis of SS with great certainty (low sensitivity, 62.50). In contrast, TBUT showed relatively high specificity (83.33), which is not in accordance with other studies[25].

These sensitivity and specificity values of TBUT were shown at marginal value of 7.5 s. Most often mentioned baseline TBUT test so far is 10 s, although in recent years value of 8 s as a border is proposed[12]. Differences between groups of subjects with SS and Sicca S was statistically significant ($p<0.008$), mean TBUT values in patients with SS were pathological (8.69 s), unlike the group with Sicca S (13.00 s).

It is obvious that these results are in line with findings from other studies, although the sensitivity values are below expectations. If the limit value TBUT rise to 10 s, the specificity of the test would fall significantly, to 50.00. Sensitivity in this case would slightly increase to approximately 69.00, which would ultimately result in significantly lower clinical usability of the test.

TBUT's modest efficacy in the differential diagnosis of SS is shown also by ROC analysis curve positioned close above the diagonal line. Area under the ROC curve was, compared with other objective ophthalmic tests, a modest 0.714. The standard error was 0.0759 with 95% confidence interval of 0.589–0.818. Results of ROC analysis in our study are congruent to results of similar studies[12].

Furthermore, in direct ROC curves comparison, TBUT showed the minimum sensitivity for the differential diagnosis of SS, right below the OSDI, whose specificity is very high (100.00). However, these differences did not show statistically significant values as to the OSDI ($p<0.783$), as when compared with Sch.1 ($p<0.318$) and Sch.2 ($p<0.159$). In accordance with these results, a clear distinction between these three tests, related to the clinical relevance in the differential diagnosis of SS, is not easy to distinguish, which contributes to the lack of precise research on this topic.

Rose Bengal score (RBS) proved to be the most efficient objective test in ophthalmic differential diagnosis for SS. Differences in values between the test group of patients with SS and Sicca S were statistically highly significant ($p<0.001$). The mean value in patients with SS was 10.56, while the same in subjects with Sicca S was 2.83. The most interesting fact of the entire study was ROC curve analysis of Rose Bengal score for a diagnosis of SS. At ideal marginal value >6, the sensitivity and specificity reached the ideal 100.00. This result is unique, although similar high values are described by other researchers[12]. ROC curve for a given variable has been removed in the leftmost position, and the area under the curve was ideal 1.000, standard error 0.000 with 95% confidence interval of 0.945–1.000. ROC curve analysis of ophthalmic tests showed the RBS as a most analytical test. The differences found between the ROC curve of RBS and other ophthalmologic tests were significant according to: OSDI ($p<0.001$), Sch.1 ($p<0.002$), Sch.2 ($p<0.003$) and TBUT ($p<0.001$).

In our, as well as in other studies[26] vital staining dye (RBS), has the highest value of the likelihood ratio, classifying it as a test of choice for SS diagnosis. Different results may be consequently to the lack of sufficient data for the test in some trials, which were performed only at fluorescein negative corneas, which would show a relatively flat curve ROC analysis[12].

In most studies, including American-European Consensus Group criteria, the item for ocular subjective symptoms only includes few simple questions concerning the common feeling of sandy eyes, eye discomfort, and use of tear substitutes. Using similar questionnaires related to sicca symptoms, previously known as the method that should be regularly used in clinical practice if there is suspicion of tear film dysfunction[27]. The total score responses to ophthalmologic symptoms, in the sense of discomfort due to dry eye, based on multiple queries, effectively distinguishes the group of patients with SS from patients with Sicca S[28]. In our study the differences between the additive values of tests were statistically significant between subjects with SS and Sicca S ($p<0.003$, Mann Whitney $U=225.00$). Mean value in the group of subjects with SS was 52.66, and in subjects with Sicca S 34.75.

Cut off value determined by ROC analysis of the test was >55.6. At the same, OSDI has a sensitivity of 56.25 and specificity of 100.00. In ROC curves analysis of studied ophthalmic tests, OSDI occupies the penultimate position, before TBUT, with the area under the ROC curve of 0.740, standard error of 0.0632 and 95% confidence interval between 0.617 and 0.840. Difference between ROC curves of OSDI and RBS is statistically significant ($p<0.001$). Compared with results of other ROC analysis, no statistically significant differences were found (compared with: Sch.1 $p<0.597$, Sch.2 $p<0.453$ and TBUT $p<0.783$).

In conclusion we can say that the OSDI questionnaire, which we used in our research[10], showed high specificity and relatively acceptable diagnostic features, indicating that the OSDI score has a certain role in clinician's orientation towards the SS diagnosis. However, this level of reliability proved to be significantly lower than the results of similar studies[27,28].
Biopsy of small salivary as one of the most analytical tests in the differential diagnosis of SS[4], confirmed the high clinical usefulness in our study. ROC analysis established very high analytical value of test, with an area under the ROC curve of 0.823, standard error of 0.0646 and 95% confidence interval of 0.709–0.906.

Depending on the attitudes of individual researchers, a biopsy is indicated if there is suspicion on final diagnosis based on clinical symptoms. However, it is important to note that the biopsy has a broader clinical utility, because it can detect other diseases, such as the sarcoidosis.

In the positive biopsy findings at Chisholm-Mason grading system[29] the sensitivity of the test was 56.25, specificity 100.00. Biopsy showed a very good, but not the best, usability in the differential diagnosis of SS. The reasons for this result may be different. One of them is certainly the way of tissue collection in which focal aggregation of lymphocytes is detected and quantified, which in our case consisted of a single section. Described »multilevel« sections[30], where results are presented as mean value of three different sections, distant at least 200 microns, in order to avoid the section of the same focus[31], could lead to an increase of the existing diagnostic value of accessory salivary glands biopsy.

Conclusion

Ophthalmic tests provide high quality clinical orientation and sometimes even the answer to the question of whether the patient has Sjøgren's syndrome or Sicca syndrome. In the absence of quality research in this area of medicine, this approach greatly contributes to the rapid diagnosis and orientation, if the tests are properly used and if it is known what each of them represents. Results from the present study show the usefulness and efficiency of implementation of the data obtained from the subjective and objective ophthalmic testing in the diagnostic criteria for SS. The results confirm the relatively poor reliability of Sch.1, OSDI and TBUT in the differential diagnosis of a SS. In contrast, same results show the test with vital color staining (RBS) as a test of choice in the differential diagnosis of a SS. Biopsy of the labial salivary glands is still considered the gold standard in diagnosis of SS and has wide clinical utility, but it is invasive and may be unpleasant method. RBS should, as non-invasive and simple test, with very high specificity and sensitivity (superior to biopsy), be performed before biopsy, as it can accurately indicate a need for further invasive investigations. We suggest making an ophthalmological tests algorithm that could distinguish patients with SS and those with Sicca syndrome without SS. Such an algorithm should contain test of vital staining color (RBS) as the most reliable ophthalmic test.

REFERENCES

1. XUE L, SUN P, Med Hypotheses, 76 (2011) 176. — 2. ROSAS GÓMEZ DE SALAZAR J, SENABRE GALLEGO JM, SANTOS RAMÍREZ C, Reumatol Clin, 6S2 (2010) 6. — 3. MANOUSSAKIS MN, MOUTSOPOULUS HM, Bailliers Best Pract Res Clin Rheumatol, 14 (2000) 73. — 4. VITALI C, BOMBARDIERI S, JONSSON R, MOUTSOPOULOS HM, ALEXANDER E, CARSONS S, DANIELS T, FOX P, FOX R, KASSAN S, PILLEMER S, TALAL N, WEISMAN M, Ann Rheum Dis, 61 (2002) 554. — 5. FLEMING COLE N, TOY EC, BAKER B, Prim Care Update Ob Gyns, 8 (2001) 48. — 6. BAMBA R, SWEISS NJ, LANGERMAN AJ, TAXY JB, BLAIR EA, Laryngoscope, 119 (2009) 1922. — 7. MCKOWN RL, WANG N, RAAB RW, KARNATI R, ZHANG Y, WILLIAMS PB, LAURIE GW, Exp Eye Res, 88 (2009) 848. — 8. PRAUSE JU, Clin Exp Rheumatol, 7 (1989) 141. — 9. LEMP MA, CLAO J, 21 (1995) 221. — 10. VITALE S, GOODMAN LA, REED GF, SMITH JA, Health Qual Life Outcomes, 2 (2004) 44. — 11. VITALI C, MOUTSOPOULOS HM, BOMBARDIERI S, Ann Rheum Dis, 53 (1994) 637. — 12. VERSURA P, FRIGATO M, CELLINI M, MULE R, MALAVOLTA N, CAMPOS EC, Eye, 21 (2007) 229. — 13. KUMAR R, INDRAYAN A, Indian Pediatr, 48 (2011) 277. — 14. PEJDA S, ALAJBEG I, ALAJBEG IŽ, Lijec Vjesn, 133 (2011) 180. — 15. PORTER SR, VUČIĆEVIĆ-BORAS V, Acta Stomatol Croat, 41 (2007) 95. — 16. VIDOVIĆ JURAS D, LUKAČ J, CEKIĆ-ARAMBAŠIN A, VIDOVIĆ A, CANJUGA I, SIKORA M, CAREK A, LEDINSKY M, Coll Antropol, 34 (2010) 1039. — 17. ALAJBEG I, HLADKI N, ALAJBEG ŽI, ROŠIN-GRGET K, VUČIĆEVIĆ-BORAS V, CEKIĆ-ARAMBAŠIN A, Period Biol, 107 (2005) 67. — 18. ALAJBEG I, HLADKI N, CEKIĆ-ARAMBAŠIN A, ALAJBEG IŽ, Acta Stomatol Croat, 37 (2003) 296. — 19. STRIETZEL FP, LAFAURIE GI, MENDOZA GR, ALAJBEG I, PEJDA S, VULETIĆ L, MANTILLA R, FALCÃO DP, LEAL SC, BEZERRA AC, TRAN SD, MÉNARD HA, KIMOTO S, PAN S, MARTÍN-GRANIZO RA, LOZANO ML, ZUNT SL, KRUSHINSKI CA, MELILLI D, CAMPISI G, PADERNI C, DOLCE S, YEPES JF, LINDH L, KORAY M, MUMCU G, ELAD S, ZEEVI I, BARRIOS BC, LÓPEZ SÁNCHEZ RM, BEISKI BZ, WOLFF A, KONTTINEN YT, Arthritis Rheum, 63 (2011) 180. — 20. HAGA HJ, HULTEN B, BOLSTAD AI, ULVESTAD E, JONSSON R, J Rheumatol, 26 (1999) 604. — 21. NICHOLS KK, MITCHELL GL, ZADNIK K, Cornea, 23 (2004) 272. — 22. HAY EM, THOMAS E, PAL B, HAJEER A, CHAMBERS H, SILMAN AJ, Ann Rheum Dis, 57 (1998) 20. — 23. PARKIN B, CHEW JB, WHITE VA, GARCIA-BRIONES G, CHHANABHAI M, ROOTMAN J, Ophthalmology, 112 (2005) 2040. — 24. XU KP, KATAGIRI S, TAKEUCHI T, TSUBOTA K, J Rheumatol, 23 (1996) 76. — 25. TSUBOTA K, TODA I, YAGI Y, OGAWA Y, ONO M, YOSHINO K, Cornea, 13 (1994) 202. — 26. HYON JY, LEE YJ, YUN PY, Cornea, 26 (2007) S13. — 27. BRUN JG, JACOBESN H, KLOSTER R, CUIDA M, JOHANNESEN AC, HØYERAAL HM, JONSSON R, Clin Exp Rheumatol, 12 (1994) 649. — 28. BOWMAN SJ, BOOTH DA, PLATTS RG, FIELD A, ROSTRON J, UK SJÖGREN'S INTEREST GROUP, J Rheumatol, 30 (2003) 1259. — 29. VERED M, BUCHNER A, HAIMOVICI E, HISS Y, DAYAN D, J Oral Pathol Med, 30 (2001) 7. — 30. MORBINI P, MANZO A, CAPORALI R, EPIS O, VILLA C, TINELLI C, Arthritis Res Ther, 7 (2005) 343. — 31. AL-HASHIMI I, WRIGHT JM, COOLEY CA, NUNN ME, J Oral Pathol Med, 30 (2001) 408. — SÁNCHEZ GUERRERO J, PÉREZ DOSAL MR, CÁRDENAS VELÁZQUEZ F, PÉREZ REQUERA A, CELIS AQUILAR E, SOTO ROJAS AE, AVILA CASADO C, Rheumatology, 44 (2005) 235.

I. Knezović

University of Zagreb, Dubrava University Hospital, Department of Ophthalmology, Avenija Gojka Šuška 6, 10000 Zagreb, Croatia
e-mail: i_knezovic@yahoo.com

DIFERENCIJALNO DIJAGNOSTIČKA UČINKOVITOST ROSE BENGAL SCORE TESTA U PACIJENATA SA SJÖGRENOVIM SINDROMOM

S A Ž E T A K

Cilj istraživanja bio je procijeniti kliničku vrijednost Rose Bengal testa pri diferencijalnoj dijagnozi Sjøgrenovog sindroma (SS), te napraviti usporedbu s ostalim provedenim oftalmološkim i salivarnim testovima. Svim sudionicima učinjeno je: mjerenje nestimulirane (UWS) i stimulirane salivacije (SWS), biopsija žlijezda slinovnica (LGB ili focus score), oftalmološki upitnik (OSDI) i objektivni testovi: Schirmer test 1 (Sch.1), Schirmer test 2 (Sch.2), Tear Break-up Time (TBUT) test i Rose Bengal test (RBS). Podaci su analizirani pomoću Mann Whitney U-testa, ROC analize, uz izračunane specifičnosti i osjetljivosti, i Spearmanovog testa korelacije. ROC krivulje pokazale su slabije dijagnostičke vrijednosti za TBUT i OSDI. Rezultati ROC analize za Sch.1, Sch.2 i LGB prikazali su dobra dijagnostička svojstva, dok je RBS imao idealne parametre (osjetljivost 100,00, specifičnost 100,00, AUC 1000) u provedenom ispitivanju. Studija otkriva slabu pouzdanost TBUT-a, OSDI-a i Sch.1, te ističe RBS kao test izbora u diferencijalnoj dijagnostici SS.