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ORIGINAL ARTICLE

The efficacy of Xialine® in patients with Sjögren's syndrome: a single-blind, cross-over study

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Abstract Sjögren syndrome (SS) is a chronic inflammatory autoimmune disease of unknown cause whose main characteristic is severe dryness of the eyes and the mouth. The decreased functional capacity of the lacrimal and salivary glands which is the result of the inflammatory process and lymphocytic infiltration observed in SS is accountable for this complication. Twenty-nine patients with SS whose ages were ranging between 24–77, who were under treatment in Ege University Faculty of Medicine Department of Rheumatology, participated in the study, and their informed consents were obtained upon enrollment. Each patient recorded their subjective complaints on a separate questionnaire. The baseline and subsequent evaluation of the subjective findings on predetermined times (1 h after application of the material, at the end of the 1st, 7th, and 14th days) were also recorded on separate questionnaire sheets. Throughout the 14-day treatment period, no statistically significant differences were noted between the Xialine® and placebo groups with regard to burning tongue, diminished taste, and waking up at night to sip water (p=0.925, 0.527, and 0.066, respectively). However, patients' satisfaction with placebo decreased by 25.63% at the end of the test period, whereas it increased by 16.37% after Xialine® administration. Overall, the patients preferred Xialine® at the end of the study (p=0.011). The main motive to administer saliva substitute is to improve lubrication and hydration of oral tissues. The results of this study indicated that Xialine® is helpful in the management of xerostomia-related symptoms of SS patients. However, further investigations in larger scale group of patients are recommended to provide the effects of these agents on various complaints of xerostomia.

Keywords Xerostomia · Sjögren's disease · Xialine · Dry mouth · Artificial saliva

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Introduction

Sjögren syndrome (SS) is a chronic inflammatory autoimmune disease of unknown cause whose main characteristic is severe dryness of the eyes (keratoconjunctivitis sicca) and the mouth (xerostomia). The decreased functional capacity of the lacrimal and salivary glands which is the result of the inflammatory process and lymphocytic infiltration observed in SS is accountable for this complication. SS predominantly affects women (the female/male ratio is approximately 9:1) and mostly observed in middle-aged individuals. There are two forms of the disease; primary SS is defined by the presence of salivary and lacrimal gland involvement alone, while secondary SS includes involvement of one or both of the exocrine sites in association with another connective-tissue disease, mostly with rheumatoid arthritis, systemic lupus erythematosus, primary biliary cirrhosis, and scleroderma [2, 10, 26].

Extremely low salivary flow rate of resting whole and parotid saliva observed in SS patients, especially in those

with primary SS, gives rise to the development of a variety of signs and symptoms such as: dental caries, periodontal disease, candidosis, glossitis, atrophy of the oral mucosa, halitosis, burning mouth, difficulty with mastication, and dysphasia [2]. Diffuse lymphoid cell infiltrates in the salivary and lacrimal glands and result in symptoms of dry mouth and eyes due to insufficient secretion. Also, apoptosis of the acinar and ductal epithelial cells of the salivary and lacrimal glands has been proposed as a possible mechanism responsible for the impairment of secretory function. Although it has been assumed that a combination of immunologic, genetic, and environmental factors may play a key role in the development of autoimmune lesions in the salivary and lacrimal glands, little is known about the disease pathogenesis of SS in humans.

Methods for screening hyposalivation include scintigraphy and sialography, both of which, while being sensitive tests for salivary gland function, are expensive and complicated [9, 11, 20, 23, 26].

On the other hand, collection of whole saliva as resting saliva per unit time performed as a chair-side analysis in the dental office is a simple and noninvasive method recommended by the Swedish Social Insurance Board [21] which has been employed in many clinical studies [2, 20].

There have been many attempts to manage the symptoms related to severe xerostomia in SS patients through the use of topical preparations and systemic medications [3, 8, 19, 28, 29, 31]. One of the topical agents is Xialine® which is a saliva substitute with visco-elastic properties closely resembling natural human saliva. The active viscoelastic component of Xialine® is the polysaccharide xanthan gum; additionally, sodium fluoride is included for mineralization of the dentition (Lommerse Pharma B.V., Oss, The Netherlands).

Although some patients have experienced benefits from these agents and treatments, a long-term relief of the symptoms has yet to be achieved. Many novel agents are being developed for the treatment of xerostomia, and their efficacies are also being investigated. The present single-blind, cross-over study aimed to evaluate the efficacy of Xialine as a saliva substitute in reducing xerostomia-related symptoms in patients with SS.

Materials and methods

Patients

Twenty nine patients with SS whose ages were ranging between 24 and 77 and who were under treatment in Ege University Faculty of Medicine Department of Rheumatology participated in the study, and their informed consents were obtained upon enrollment. These patients were diagnosed as SS according to American-European criteria. Among these, all patients were diagnosed with primary SS. All patients had a full medical history and physical examination; complete blood count, determination of erythrocyte sedimentation rate, quantitative immunoglobulins, antinuclear antibody, DNA antibody, rheumatoid factor, and hepatic and renal function analyses were performed. The presence or absence of keratoconjuctivitis sicca was established after a complete ophthalmologic evaluation and with a positive Schirmer test. All patients underwent labial biopsy, and the histopathologic grading of the labial gland specimens was performed according to the criterion of Chisholm and Mason [7]. Patients with one or more than one focus of lymphocytes per 4 mm^2 (grade 3 and 4) were diagnosed as histologically positive.

The SS patients enrolled into this study had not used any pharmaceutical agents for treatment of xerostomia prior to the study; they had sought relief of their oral symptoms only by frequent sipping of plain water.

Study design

In this cross-over, single-blind study, all patients were subjected to a thorough clinical examination, and the objective findings of each patient were recorded on a patient form (Table 1). The patients enrolled in the study had no consumption of alcohol and tobacco. Salivary flow rate of each patient was also measured as explained below.

Each patient recorded their subjective complaints on a separate questionnaire. The baseline and subsequent evaluation of the subjective findings on predetermined times (1 h after application of the material, at the end of the 1st, 7th, and 14th days) were also recorded on separate questionnaire sheets. Informed consent from each patient was obtained according to the Declaration of Helsinki.

A placebo was prepared with plain water and diluted tea in order to make it resemble Xialine®. This was poured into the empty plastic spray bottles of the saliva substitute to provide the standard appearance of the materials. The placebo closely resembled Xialine® in appearance and taste. The patients were instructed to use the placebo six times a day for 14 days. After 14 days, a wash out period of 7 days was used. Then, Xialine® was given to the patients. None of the patients knew which material was placebo; only the researchers knew what was provided to the patients.

Administration of the placebo was preferred prior to Xialine® because if Xialine® were used before the placebo, then the topical effects of Xialine® (if any) would mask the effects of the latter.

Objective measurements

The clinical evaluation of the patients were performed according to Navazesh et al. [28]. Dryness and cracking of

Table 1 Objective findings of xerostomia

Name: Address: Date:

LIP DRYNESS SCORE:

0: Dryness and cracking of the corners and/or the vermiilion borders of the lips.

1: Dry vermillion border.

2: Dry, chapped and/or fissured tissue.

3: Angular cheilitis, redness or fissuring at the commissure.

BUCCAL MUCOSA DRYNESS SCORE:

0: Normal

1: Looks dry, but the tissue does not stick to the tongue blade.

2: Looks dry, and the tissue sticks to the tongue blade.

3: Looks dry, tissue sticks to the tongue blade and the location of one or both parotid ducts is not apparent.

SALIVARY POOL SCORE:

0: Saliva accumulate on the floor of the mouth.

1: Saliva does not accumulate on the floor of the mouth.

SALIVARY GLAND PALPATION SCORE:

Evidence of major gland swelling, tenderness upon palpation, or failure of saliva to be elicited from either Wharton's or Stenson's ducts.. Flow limited to 1 or 2 drops or viscous or contaminated with blood or pus scored as having no saliva.

0: Absence of any of the above mentioned symptoms.

1: Presence of at least one of the symptoms.

SALIVARY FLOW

Non-stimulated …….ml/sec. (normal values: 0.3-0.4 ml/min)

Stimulated ……..ml/sec. (normal values: 1-2 ml/min)

the corners and/or the vermilion borders of the lips were scored as 0 (normal), 1 (dry vermilion border), 2 (dry, chapped and/or fissured tissue), or as 3 (angular chelitis, redness or fissuring at the commissure).

Dry tongue blades were used to retract the buccal mucosa bilaterally, and the mucosa was scored as 0 (normal), 1 (looks dry but tissue does not stick to the tongue blade), 2 (looks dry and tissue sticks to the tongue

blade), or as 3 (looks dry, tissue sticks to the tongue blade, and the location of one or both parotid ducts is not apparent). A tongue was scored positive for sticking if either or both cheeks stuck to the blade.

Saliva that had accumulated on the floor of the mouth was referred to as the salivary pool and was scored as 0 (absence of it or any of the above-mentioned symptoms), or 1 (symptoms present).

Subjective measurements

Via a thorough literature survey, xerostomia-related oral complications were determined beforehand, and accordingly, a patient questionnaire was prepared. The items which were presented to the patients to determine the degree of xerostomia and associated subjective complaints such as dry mouth, burning tongue and/or oral mucosa, taste impairment, difficulty in mastication/speaking, need to sip liquids to aid swallowing, and frequent need to moisten the oral mucosa were continuous (Table 2).

Each of the patients' reply was recorded on a visual analogue scale (VAS). VAS is a measurement instrument which is commonly used to measure a characteristic or an attitude that ranges across a continuum of values and cannot be directly measured [10, 13]. It is a horizontal line, 100 mm in length, anchored by verbal descriptors at each end. The left end of the line indicates the absence of that characteristic, whereas the right end represents the highest level of it. The patient marks the line at some point which best represents the perception of his/her status at that moment, and the VAS value is determined by measuring in millimeters from the left hand of the line to the point the patient marks [14].

Non-stimulated and stimulated, whole salivary flow rate measurements

Measurements were performed between 9 and 11 A.M. by spitting method. Subjects were instructed to refrain from food and beverages for 2 h before test session. Before salivary collections began, each subject rinsed thoroughly several times with de-ionized water and rested for 5 min. The subjects were asked to bend their heads forward and, after an initial swallow, to allow saliva flow into the mouth. Subjects expectorated the saliva into a test tube once per minute, for 5 min, and the flow rate was recorded as milliliter per minute. Stimulated whole saliva was recorded in a similar manner, with moderate stimulation produced by applying four drops of about 0.1 mol/l citric acid to the tongue at 15-s intervals during 1 min [7, 9].

Statistical analysis

The VAS scores of each subjective finding for each time interval were recorded both for the placebo and Xialine®. The effects of test materials with respect to treatment period were established by using area under curve (AUC) method, which is the most frequent summary measure applied in studies [1]. Thus, the variations within the efficacy of the materials throughout the study period were determined.

Since the distribution of VAS scores regarding five different treatment periods departed from normal distribution, nonparametric analysis was preferred, and Wilcoxon signed-rank test was applied to compare the subjective responses of the patients to the placebo and Xialine®. Friedman tests were applied to observe the changes between each time interval. In all tests, SPSS for Windows was used and p was set as 0.05.

Results

In this study, the mean age of 29 patients was 45. Their mean unstimulated whole salivary flow (WSF) rate was 0.15 ml/s, and the mean stimulated rate was recorded as 0.34 ml/s. Both salivary flow rates were below the normal values, considering the normal unstimulated WSF as ranging between 0.3 and 0.4 ml/s, and the stimulated WSF rate as ranging between 1 and 2 ml/s. The objective findings of the patients which approved the presence of xerostomia are illustrated in Table 3.

The scores which were recorded for each question of the questionnaire at five different time intervals (baseline, after 1 h, and at the end of the 1st, 7th, and the 14th days) of the treatment for Xialine® and placebo groups are shown in Table 4.

The answers to the questionnaire showed that for each time interval, there were statistically significant changes over all of the xerostomia-related complaints both within the placebo and Xialine® group($p>0.05$, $p=0.000$, respectively).

When the changes within the VAS scores of each treatment material were examined at the end of the study,

Table 2 Objective findings observed in SS patients

	Lip dryness				Buccal mucosa dryness				Salivary pool		Salivary gland palpation	
Scores	0	1	2	3	0	1	2	3	0	1	0	1
N	7	15	5	2	2	19	8	0	4	25	1	28

Table 3 Subjective findings of xerostomia

Findings
Continuous dry mouth
Burning tongue
Painful oral mucosa
Diminished taste
Difficulty in mastication
Difficulty in swallowing
The need to sip liquids to aid swallowing
Difficulty in speaking
Dryness at night or awakening
Frequent need to moisten oral mucosa
Efficacy of the treatment

it was found that placebo VAS scores showed an amelioration of the condition (in other words, relief of the complaints) in the questions regarding continuous dry mouth (25.42%), difficulty in mastication (27.25%), difficulty in swallowing (28.95%), the need to sip liquids to aid swallowing (43.98%), difficulty in speaking (39.61%), dryness at night or awakening (35.24%), and frequent need to moisten oral mucosa (33.78%). On the other hand, VAS scores increased in questions (worsening of the condition) searching for burning tongue (14.51%), painful oral mucosa (3.71%), and diminished taste (4.89%). At the end of the placebo administration, patients' satisfaction with the agent decreased by 25.63%.

Xialine VAS scores revealed a decrease in the burning tongue complaint at the end of the treatment (21.04%). Likewise, all other parameters significantly improved [continuous dry mouth (4.78%); painful oral mucosa (3.93%); diminished taste (25.12%); difficulty in mastication (37.39); difficulty in swallowing (20.93%); the need to sip liquids to aid swallowing (22.95%); difficulty in speaking (2.38%); dryness at night or awakening (2.54%); and frequent need to moisten oral mucosa (3.24%)]. At the end of the Xialine administration, patients' satisfaction with the agent increased by 16.37%.

The question which was administered to evaluate the treatment's effectiveness showed that the VAS scores provided for the efficacy of the placebo and Xialine® were significantly different, and Xialine® group was more satisfied with the treatment at the end of the study (p=0.011). The values obtained by AUC method showed that patients' satisfaction with Xialine® administration started to increase on the seventh day and lasted steadily until the end of the study when compared to the placebo treatment (p=0.008).

Likewise, patient's complaints concerning mastication, swallowing, daily liquid consumption, mouth burning, the need to sip liquids to aid swallowing, and difficulty in speaking decreased in the Xialine® group (p=0.06; 0.027; 0.019; 0.025; 0.023; and 0.004, respectively) (Table 4).

Table 4 The values of the placebo and Xialine® groups at different intervals of the study regarding the symptoms of xerostomia

Symptom and visit	Mean VAS scores	
	Placebo	Xialine
Continuous dry mouth		
Baseline	50.702	34.183
1st hour	53.503	32.747
1st day	45.309	36.869
7th day	41.735	32.443
14th day	37.811	32.548
Burning tongue		
Baseline	18.525	19.515
1st hour	12.592	15.824
1st day	19.268	21.453
7th day	16.906	19.542
14th day	21.214	15.410
Painful oral mucosa		
Baseline	15.325	18.007
1st hour	9.497	15.997
1st day	19.189	16.667
7th day	16.875	10.608
14th day	15.893	10.927
Diminished taste		
Baseline	8.787	13.636
1st hour	6.994	12.581
1st day	12.133	14.705
7th day	15.421	13.742
14th day	9.217	10.211
Difficulty in mastication		
Baseline	26.967	17.856
1st hour	8.284	14.062
1st day	19.123	16.930
7th day	24.999	15.328
14th day	19.618	11.180
Difficulty in swallowing		
Baseline	42.056	24.261
1st hour	29.462	18.226
1st day	34.565	23.054
7th day	35.508	21.148
14th day	29.879	19.182
The need to sip liquids to aid swallowing		
Baseline	43.813	26.601
1st hour	19.907	25.547
1st day	34.741	27.295
7th day	31.828	24.785
14th day	24.545	20.496
Difficulty in speaking		
Baseline	36.395	15.934
1st hour	16.367	18.993
1st day	22.108	19.835
7th day	26.966	19.194
14th day	21.980	15.555
Dryness at night or awakening		
Baseline	32.928	21.044
1st hour	15.969	24.901
1st day	32.765	24.495
7th day	28.154	20.098

Table 4 (continued)

Symptom and visit	Mean VAS scores	
	Placebo	Xialine
14th day	21.324	20.509
Frequent need to moisten oral mucosa		
Baseline	57.339	31.189
1st hour	33.994	26.160
1st day	46.964	32.992
7th day	40.883	30.989
14th day	37.972	30.069
Efficacy of the treatment		
1st hour	18.921	22.158
1st day	22.126	23.911
7th day	17.711	24.744
14th day	14.071	25.786

The question which was determining the patients' mouth dryness showed that, although not statistically significant (p=0.061), more patients had relief over their xerostomia complaints at the end of the treatment with Xialine® when compared to placebo group.

Throughout the 14-day treatment period, no statistically significant differences were noted between the Xialine® and placebo groups with regard to burning tongue, diminished taste, waking up at night to sip water (p= 0.925; 0.527; and 0.066, respectively). In other words, Xialine® and placebo were equally effective concerning the above-mentioned subjective parameters (Fig. 1).

Discussion

This cross-over, single-blind study investigated the efficacy of Xialine® and a placebo on a group of SS patients who experience xerostomia. Although rarely, clinical evaluation of the patients with xerostomia complaints may fail to reveal salivary dysfunction, or some patients with severe mouth dryness may not have severe clinical complaints

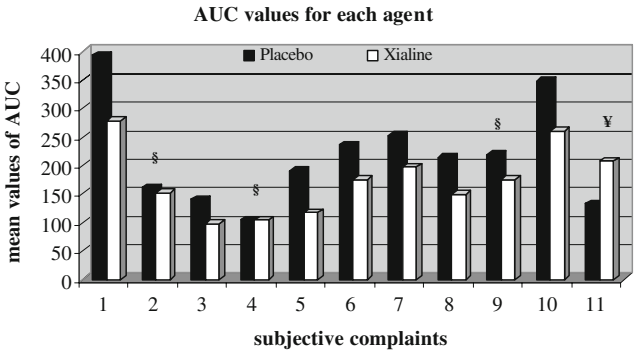

Fig. 1 The AUC values of the materials each regarding the efficacy of the agents throughout the study period. § Not significant (p>0.05). ¥: The efficacy of the test materials at the end of treatment

[5, 9, 24, 25, 28, 32]. Therefore, in order to make sure that the participants had diminished salivary function, the unstimulated/stimulated salivary flow rates and objective findings of xerostomia were also established for each patient, and the existence of xerostomia was confirmed objectively.

Management of xerostomia is important for the patient's quality of life and may prevent consequent oral diseases [3, 12, 20, 26, 29, 30]. Whenever possible, stimulation of residual salivary gland function should be attempted [20, 22, 31, 34]. However if adequate salivary production cannot be achieved, then palliative measures with saliva substitutes may be considered. This pilot study was performed to investigate whether the use of Xialine® provided an improvement in xerostomia-related symptoms when compared with a placebo. The Xialine®-using patients practiced statistically less symptoms of xerostomia, and after the first week of the treatment, the decrease in the VAS scores of this group indicated an improvement in xerostomia-related symptoms.

Since xerostomia has a dynamic and changing nature and is a subjective clinical phenomenon, studies investigating the degree of xerostomia and the efficacy of its treatment rely heavily on self-reported data [18]. VAS is a self-reported measuring tool that is commonly used to establish subjective parameters such as pain, psychological dimensions, analgesic effects of pharmaceuticals, etc. [4, 13, 36, 38, 39, 41]. However, subjective responses may be influenced by personal, emotional, and environmental factors and may show variations among the individuals as observed in our study [2]. The uneven distribution of the VAS scores provided for the same parameter by the patients (such as the level of xerostomia) has led to problems in statistical analysis of data. Initially, VAS was preferred in order to provide numeric values for the analyses. However, our data greatly departed from normal distribution, and we had to use nonparametric tests for statistical analyses. The nonparametric methods in analysis of variance (ANOVA) are based on the analysis of ranks of observations rather than the original observations. When more than two related samples are of interest, Friedman two-way ANOVA by ranks test is preferred. Here, two refers to (1) levels of the treatment and (2) the repeated occasions on which the subjects were observed [33].

In this cross-over study, each patient used both of the study products to reduce the variations due to patient factors [33]. Additionally, as an attempt to raise the chances to reach an accurate conclusion, the subjects served as their own controls, and repeated measurements provided by each patient were obtained. It is known that repeated measurements are, by their own nature, multidimensional (a patient has multiple pain evaluations in time); for this reason, rather than data analysis at each time interval, summary measures analyses were preferred [6, 33].

Our results revealed the competence of both test materials on eliminating xerostomia and its related complaints. In other words, both placebo and Xialine® caused significant improvement at the end of treatment when compared to the beginning of the trial. As mentioned previously, the placebo in our study was plain water. In the literature, frequent sipping of water has been reported as one of the common methods to treat dry mouth [8, 15, 22, 37, 40]. Our findings also confirmed the previous reports and emphasized the importance of wetting the oral mucosal surface to provide relief from xerostomia.

Many saliva substitutes have been recommended as the topical treatment agents of xerostomia. Among those, Luborant®, Saliva Orthana®, Salivace®, Glandosane®, Biotene®, Oralube®, and Oral Balance® are most examined proprietary agents and have revealed various degrees of efficacy in vivo and in vitro [3, 29, 31, 32, 35]. Problems related with speech/mastication and sipping water to aid swallowing were reported as the major diagnostic manifestations of Sjögren's syndrome [29]. When all questions were evaluated, Xialine® was found to be statistically effective on these Sjögren's syndrome symptoms, especially beginning at the end of the first week and constantly ongoing till the end of the study. In accordance with our findings, the competence of Xialine® for the relief of xerostomia-related complaints in patients with SS has been reported by Jellema et al. [19]. They have shown higher improvement with regard to problems of speech and decreased senses when Xialine® was used. However, its efficacy was not significantly different than that of placebo with respect to xerostomia, sticky saliva, and social eating [19]. In that study, it was declared that addition of xanthan gum was the sole difference between placebo and Xialine®.

Xanthan gum is a natural gum polysaccharide and is used as a food additive and rheology modifier. It is produced by the *Xanthomonas campestris* bacterium, and due to its pseudoplastic properties, it can seem thin in the mouth but still have good stabilization properties [16]. It is mainly used for the control of viscosity, and its most important property is its very high low-shear viscosity coupled with its strongly shear-thinning character. The relatively low viscosity at high shear means that it is easy to mix, pour, and swallow, but its high viscosity at low shear gives good suspension and coating properties and lends stability to colloidal suspensions [17].

The viscosity of human saliva was found to be inversely proportional to shear rate, which was defined as a non-Newtonian trait [28]. So, salivary substitutes are expected to have a viscoelastic pattern similar to normal human saliva to provide similar viscosity and film forming properties [8, 28]. These features may explain why xanthan gum-containing saliva substitutes have shown synergistic effects on the elastic and rheologic properties of human whole saliva [19].

The main motive to administer saliva substitute is to improve lubrication and hydration of oral tissues, to boost the life quality of xerostomia patients (especially the ones with dentures), to offer appropriate remineralizing and/or erosion-preventing effects, and to provide optimum oro-dental health [26, 31, 38]. The results of this study indicated that Xialine® can be applied as a helpful aid in the management of xerostomia-related symptoms of SS patients. However, further investigations in larger scale group of patients are recommended to provide the effects of these agents on various complaints of xerostomia.

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