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Original article

Sialendoscopy increases saliva secretion and reduces xerostomia up to 60 weeks in Sjögren's syndrome patients: a randomized controlled study

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Abstract

Objective. To assess the effect of sialendoscopy of the major salivary glands on salivary flow and xerostomia in patients with Sjögren's syndrome (SS).

Methods. Forty-five patients with SS were randomly assigned to a control group (no irrigation, control, $n = 15$), to irrigation of the major salivary glands with saline (saline, $n = 15$) or to irrigation with saline followed by corticosteroid application (triamcinolone acetonide in saline, saline/TA, $n = 15$). Unstimulated whole saliva flow (UWSF), chewing-stimulated whole saliva flow (SWSF), citric acid-stimulated parotid flow, Clinical Oral Dryness Score (CODS), Xerostomia Inventory (XI) and EULAR SS Patient Reported Index (ESSPRI) scores were obtained 1 week before (T0), and 1, 8, 16, 24, 36, 48 and 60 weeks after sialendoscopy. Data were analysed using linear mixed models.

Results. Irrespective of the irrigation protocol used, sialendoscopy resulted in an increased salivary flow during follow-up up to 60 weeks. Significant between-group differences in the longitudinal course of outcomes were found for UWSF, SWSF, XI and ESSPRI scores ($P = 0.028$, $P = 0.001$, $P = 0.03$, $P = 0.021$, respectively). UWSF at 60 weeks was higher compared with T0 in the saline group (median: 0.14 *vs* median: 0.10, $P = 0.02$) and in the saline/TA group (median: 0.20, *vs* 0.13, $P = 0.035$). In the saline/TA group SWSF at 48 weeks was higher compared with T0 (median: 0.74 *vs* 0.38, $P = 0.004$). Increase in unstimulated salivary flow was also reflected in improved CODS, XI and ESSPRI scores compared with baseline.

Conclusion. Irrigation of the major salivary glands in patients with SS increases salivary flow and reduces xerostomia.

Key words: Sjögren's syndrome, endoscopy, saliva, xerostomia, salivary glands

Introduction

Sjögren's syndrome (SS) is an autoimmune disorder causing chronic inflammation and irreversible exocrine gland damage. The mononuclear infiltrates and IgG plasma cells in salivary glands that lead to irreversible destruction of glandular tissue are a characteristic of SS [1]. Salivary flow gradually reduces in patients with SS [2]. Hyposalivation experienced by these individuals underlies xerostomia (sensation of oral dryness) as well as problems with speech, swallowing and eating. Patients with SS are at risk of developing oral mucosal inflammation and progressive dental decay [3].

Systemic treatments used for SS are accompanied by side effects, are ineffective, or both [4]. Some biologic disease-modifying anti-rheumatic drugs have shown potential to increase salivary flow with mostly mild adverse events [5]. These biologics will likely only be effective for subgroups of SS patients [6].

A recent case series, two pilot studies and a randomized clinical trial showed that salivary gland function was improved and oral SS symptoms were alleviated after sialendoscopy of the major salivary glands [7–10]. Sialendoscopy is an endoscopic diagnostic tool for the major salivary glands and is also

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CLINICAL SCIENCE

Rheumatology key messages

- No agent is available to treat hyposalivation and xerostomia effectively in Sjögren's syndrome patients.
- Sialendoscopy results in an increased salivary flow and reduced xerostomia up to 60 weeks.

used to treat stricture-, mucus plug- and sialolith-associated chronic obstructive salivary diseases [11–15]. Patients affected by salivary gland inflammatory disease and xerostomia report fewer symptoms after irrigation of the ductal system with saline or a combination of saline and corticosteroid [7–10].

We already reported the short- and medium-term results of sialendoscopy in SS [8, 10], but the long-term effects on salivation and xerostomia are not yet known. We hypothesized that sialendoscopy-assisted irrigation and dilatation of strictures in the ducts of the major salivary glands in patients with SS could increase unstimulated whole saliva flow (UWSF) and chewing-stimulated whole saliva flow (SWSF) as well as improve reported mouth feel up to at least 1 year after treatment. Therefore, the aim of this study was to assess long-term effects of the use of sialendoscopy with saline or sialendoscopy with saline followed by saline/corticosteroid irrigation on salivary gland function and sensation of oral dryness compared with a non-treatment control group.

Methods

Study population

The study population consisted of patients with SS (age: 18–75 years) with baseline UWSF >0.0 ml/min or evidence of glandular reserve function (SWSF ≥ 0.02 ml/min). Each patient included in the study population met the 2002 AECG classification criteria [16]. Participants were recruited from the Drymouth Outpatient Clinic Amsterdam, through rheumatologists from the Amsterdam University Medical Center (AUMC) and with help from the Dutch Society for Sjögren's Syndrome Patients.

Patients were excluded from the study population if they had a severe illness, acute sialadenitis, a history of head or neck radiotherapy or a physical condition that did not allow the use of general anaesthesia during treatment. Sialogogue use was also prohibited. The AUMC Research Ethics Board approved the study protocol (no. NL44018.029.13). The study was performed in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonization on Good Clinical Practice, and the applicable Dutch regulatory requirements. Written informed consent was obtained from each patient.

Study design

The study groups were a non-intervention control group ($n=15$) and two sialendoscopy (intervention) groups. The two intervention groups were endoscopic irrigation of the ductal system with saline ($n=15$) or saline followed by application of 40 mg/ml triamcinolone acetonide (TA; Kenacort-40, Bristol-Myers-Squibb, New York, NY, USA) in 5 ml saline (saline/TA) just before completion of sialendoscopy ($n=15$). Controls were not blinded to allocation to the non-intervention group because use of blinding for this group would have required addition of a sham sialendoscopy, which did not receive permission from the Research Ethics Board. Participants in the intervention groups were blinded to the therapeutic intervention (saline *vs* saline/TA).

In all groups, UWSF, SWSF and 2% w/v citric acid-stimulated parotid flow (SPF) were collected during eight appointments [1 week before intervention (T0), and 1 (T1), 8 (T8), 16 (T16), 24 (T24), 36 (T36), 48 (T48) and 60 (T60) weeks after sialendoscopy]. Clinical Oral Dryness Score (CODS) [17], Xerostomia Inventory (XI) [18] and EULAR SS Patient Reported Index (ESSPRI) [19] scores were recorded at every appointment. The study protocol is registered at ClinicalTrials.gov (no. NCT02112019). The design and reporting of this study are consistent with CONSORT statement recommendations [20].

Randomization

We used blocked randomization to form the allocation list for the three comparison groups. We used a random number generator (www.randomizer.org) and random block sizes. The investigator performing the baseline and follow-up assessments was blinded for the treatment received by the patient.

Outcome measures

Sialometry

Each patient was instructed to refrain from drinking, eating or chewing, brushing teeth, and smoking for 90 min before each visit. To minimize diurnal variation, the appointments for each patient were at the same time of the day and in the same room (temperature $21 \pm 2^{\circ}$C, humidity 50–60%). UWSF and SWSF samples were collected into separate pre-weighed containers every 30 s during 5 min. For the UWSF samples, each patient was instructed to start collecting saliva immediately after an initial swallow and then expectorate. For the SWSF samples, patients were instructed to chew a 5×5 cm sheet

of paraffin (Parafilm M, Pechiney, Chicago, IL, USA) and then expectorate every 30 s. Each container was reweighed after saliva collection and the weight of the empty container was subtracted to determine UWSF and SWSF flow rates (ml/min) [21]. Parotid-stimulated saliva was collected from each parotid gland using modified Lashley cups. Citric acid (2% w/v) was applied to the lateral border of the tongue using a cotton wool swab at 30-s intervals to stimulate parotid gland secretion [22]. The same observer (F.M.) performed all assessments, blinded to the therapeutic intervention (saline *vs* saline/TA) and condition of the patients.

CODS

The CODS is a validated clinical guide designed to assess oral dryness using clinical and visual inspection of the oral cavity. It includes 10 clinical signs of oral dryness, such as the presence of frothy saliva and stickiness of the dental mirror to the tongue [17, 23]. The values from the items were summed to result in a score ranging from 0 (no oral dryness) to 10 (extreme oral dryness).

XI

The summated XI is an 11-item validated questionnaire about oral dryness and mouth feel. A five-point Likert scale is used to indicate symptom frequency. The values from the items were summed to give a total XI score of 11 (no dry mouth) to 55 (extremely dry mouth) [18].

ESSPRI

Disease symptoms (pain, fatigue, dryness) were assessed using a 10-point scale patient-administered questionnaire. The ESSPRI has high sensitivity for detection of changes in symptoms after a therapeutic intervention is performed. Only the dryness domain was included in the analysis. A change of two or more points was considered clinically relevant [19].

Intervention

All sialendoscopies were performed by one experienced surgeon (K.H.K.). Erlangen sialendoscopes (Karl Storz GmbH & Co, Tuttlingen, Germany) were used to perform the procedures. To standardize treatments among patients, each sialendoscopy was performed under general anaesthesia.

The parotid and submandibular gland ductal systems were irrigated using saline or saline followed by saline/TA at the end of the sialoendoscopic procedure. The saline/TA solution was injected intraductally under direct vision and maintained in the glands for 10 min by temporarily occluding the ductal orifices using a microvascular clamp. Hydrostatic pressure was used to dilate strictures.

Sample size and statistical analysis

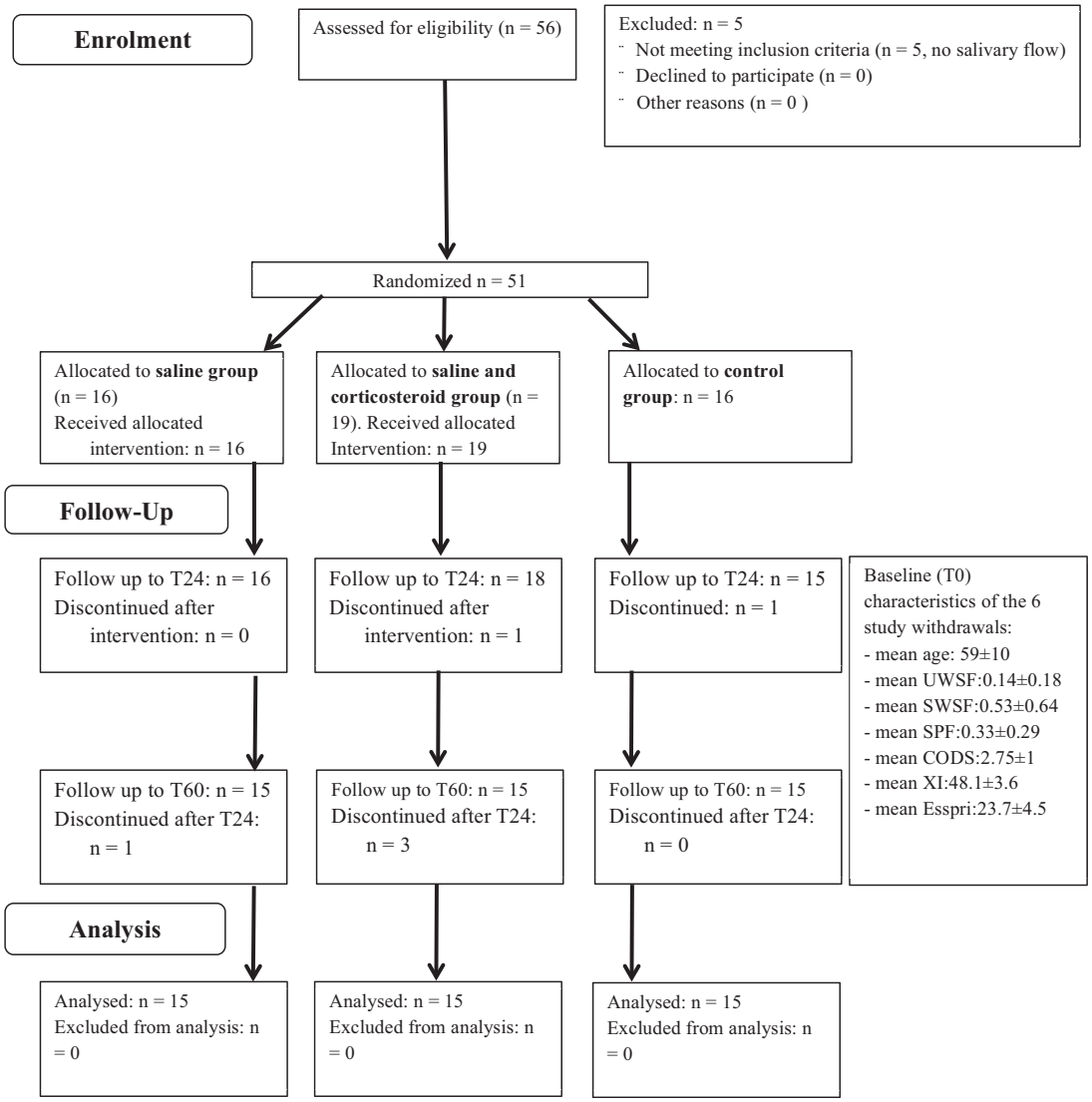
A sample size of 14 patients per group was calculated based on the results of a previously performed study [8, 24]. Mean and standard deviation are reported for data with a normal distribution. Median and interquartile range (IQR) are reported for data with a non-normal distribution. Additionally, mean and standard deviation are also reported for non-normally distributed data to clarify relatively small differences and to make comparisons with existing literature possible. A square root transformation was performed for UWSF, SWSF and SPF in order to achieve normality of residuals for application of linear mixed models. No transformation was needed for CODS, XI and the dryness domain of ESSPRI. A linear mixed model was used to compare the longitudinal course of the outcomes between the three groups. Models contained a random effect for subject and fixed effects for treatment group (three groups) and time point (baseline and seven follow-up time points) and the interaction of treatment group and time point. In cases for which the interaction was significant, we performed *post hoc* tests in which we compared outcomes for the two experimental treatments with the control treatment at the separate time points. In addition we performed *post hoc* tests in which we compared outcomes within each treatment group at each follow-up time to baseline. A Bonferroni adjustment was applied to *P*-values of *post hoc* tests in order to account for multiple testing. Data were analysed using SPSS version 23.0 (IBM Corp, Armonk, NY, USA). A *P*-value of 0.05 or lower was considered statistically significant.

Results

Forty-five patients completed the study between July 2014 and December 2017 (last follow-up). At the start of the study, we randomized 51 patients [10]. During follow-up, between 24 and 60 weeks, two patients were lost because they moved too far from the trial site, one patients because of grandchild care responsibilities and one patient lost interest in the study. Only data from patients with a complete follow-up period were used in a per-protocol analysis (Fig. 1). The baseline characteristics of all the withdrawals between time of inclusion and T60 are presented in Fig. 1. Characteristics of the study population are presented in Table 1. The overall rate of complications was limited and the most occurring complication was unsuccessful identification or dilatation of the ductal papilla. Especially we were not able to get access to Wharton's duct and thereby the submandibular gland. In the saline group 56.7% (17 of 30 ducts) of Wharton's ducts were accessible. In the saline/TA group this was 36.7% (11 of 30 ducts). To investigate whether glands in either primary SS (pSS) or secondary SS (sSS) patients were more or less accessible we divided the study population into a pSS and sSS group. Wharton's duct was accessible in 19 of 46 (41.3%) of the glands affected by pSS. In glands affected by sSS this was 9 of 14 (64.3%). In cases of obstruction of one or more of the salivary glands orifices, the sialendoscopic procedure was performed in the remaining available open salivary gland orifices.

During sialendoscopy, strictures were present (Supplementary Video, available at *Rheumatology* online) removed for all treated salivary glands by dilatation.

Fig. 1 Flow diagram of the allocation of participants to the various treatment groups



CODS: Clinical Oral Dryness Score; ESSPRI: EULAR SS Patient Reported Index; SPF: citric acid-stimulated parotid flow; SWSF: chewing-stimulated whole saliva flow; T0: 1 week before intervention; T1, T8, T16, T24, T36, T48, T60: 1, 8, 16, 24, 36, 48 and 60 weeks after sialendoscopy, respectively; UWSF: unstimulated whole saliva flow; XI: Xerostomia Inventory.

Baseline comparison of the groups revealed no significant differences in outcome measures. When we divided the participants into responders and non-responders and subsequently compared the baseline median UWSF and SWSF values of the responders and non-responders, no statistically significant differences were found ($P > 0.05$).

The results are presented in Table 2 and Fig. 2A and B.

Between-group analyses

The longitudinal course of UWSF and SWSF was found to differ significantly between the three groups (*P*-value for interaction: $P = 0.028$ and $P = 0.001$, respectively). In a *post hoc* analysis, no specific time points were identified at which UWSF and SWSF in the experimental groups differed significantly from the control group.

Also the longitudinal course of the XI was found to differ significantly between the groups (*P*-value interaction: $P = 0.03$). In a *post hoc* analysis, XI scores for both intervention groups were found to be significantly lower ($P < 0.05$) compared with the control group from T16 onwards.

Finally, the longitudinal course of the dryness domain of ESSPRI was found to differ significantly between the groups (*P*-value interaction: $P = 0.021$). In a *post hoc* analysis, scores for the saline group were found to be already significantly lower compared with the control

Table 1 Characteristics of the study population and baseline values for all parameters

Characteristic	Mean (s.d.) or n (%)	Median (IQR)
Patient variables		
Age, mean (s.d.), years	58 (9.3)	52.4 (54–65.9)
Female gender, *n* (%)	40 (88.9)	
Disease duration, mean (s.d.), years[a]	9.8 (9.0)	7 (3–13)
Control group	10.1 (9.0)	7 (3–21)
Saline group	8.5 (9.3)	7 (3–9)
Saline/TA group	10.9 (9.2)	11 (3–16)
Primary SS, *n* (%)[b]:	32 (71.1)	
Control group	9 (60)	
Saline group	13 (86.7)	
Saline/TA group	10 (66.7)	
Secondary SS, *n* (%)[b]:	13 (28.8)	
Control group	6 (40)	
Saline group	2 (13.3)	
Saline/TA group	5 (33.3)	
Autoantibodies to anti-SSA or anti-SSB, *n* (%)	39 (86.7)	
Positive salivary gland biopsy, *n* (%)	35 (77.8)	
Objective ocular involvement (Schirmer's test), *n* (%)	43 (95.6)	
Baseline UWSF, mean (s.d.), ml/min	0.14 (0.15)	0.1 (0.05–0.19)
Control group	0.13 (0.11)	0.09 (0.03–0.18)
Saline group	0.15 (0.21)	0.1 (0.03–0.19)
Saline/TA group	0.15 (0.11)	0.13 (0.06–0.2)
Baseline SWSF, mean (s.d.), ml/min	0.45 (0.43)	0.3 (0.13–0.7)
Control group	0.48 (0.46)	0.25 (0.15–0.73)
Saline group	0.35 (0.40)	0.22 (0.07–0.61)
Saline/TA group	0.50 (0.43)	0.38 (0.13–0.75)
Baseline SPF, mean (s.d.), ml/min	0.19 (0.22)	0.10 (0.0–0.29)
Control group	0.21 (0.21)	0.17 (0.00–0.47)
Saline group	0.17 (0.25)	0.1 (0.00–0.2)
Saline/TA group	0.20 (0.21)	0.1 (0.02–0.4)
Xerostomia Inventory	44.1 (6.3)	
ESSPRI (all domains)[c]	6.6 (1.63)	
ESSPRI (dryness domain)	7.56 (1.56)	
Clinical Oral Dryness Score	2.78 (1.17)	
Gland variables, *n* (%)		
Glands accessible and rinsed saline group	45 (75)	
Parotid glands	28 (93.3)	
Submandibular glands	17 (56.7)	
Glands accessible and rinsed saline/TA group	39 (65)	
Parotid glands	28 (93.3)	
Submandibular glands	11 (36.7)	

Mean (s.d.) and median (interquartile range; IQR) values are presented for data with a non-normal distribution. [a]Disease duration is years since diagnosis. [b]Classified according the 2002 American European Consensus Group Criteria (AECG); all patients classified as secondary SS had rheumatoid arthritis. [c]Defined as the total ESSPRI score divided by 3. ESSPRI: EULAR SS Patient Reported Index; SPF: citric acid-stimulated parotid flow; SS: Sjögren's syndrome; SWSF: chewing-stimulated whole saliva flow; TA: triamcinolone acetonide; UWSF: unstimulated whole saliva flow.

group from T1 onwards. Scores for the saline/TA group were found to be significantly lower compared with the control group from T8 onwards.

Longitudinal courses of SPF and CODS were not found to differ between treatment groups (*P*-value interaction: 0.075 and 0.71, respectively).

Within-group analyses: saline group

Over time, UWSF increased up to T60 compared with T0. UWSF differed significantly between time points [$F(7,294) = 3.319$, $P = 0.002$]. *Post hoc* tests showed UWSF to be increased at T8 compared with T0 ($P = 0.032$). In addition, significant increases compared with baseline were found at T24 and T36. Also at 60 weeks UWSF (median: 0.14 ml/min) was still higher compared with T0 ($P = 0.020$).

Mean CODS decreased after intervention and was found to differ significantly between time points [$F(7,293) = 3.222$, $P = 0.003$]. *Post hoc* tests revealed that CODS decreased by an average of 1.27 (95% CI:

Table 2 Results of all outcome measures for all groups at baseline and subsequent time points

	Control group			Saline group				Saline/TA group			
	Median (IQR)	Mean (S.D.)	*P*-value (compared to baseline)	Median (IQR)	Mean (S.D.)	*P*-value (compared to baseline)	*P*-value (compared to control)	Median (IQR)	Mean (S.D.)	*P*-value (compared to baseline)	*P*-value (compared to control)
UWSF, ml/min											
T0	0.09 (0.03–0.18)	0.13 (0.11)	1.00	0.10 (0.03–0.19)	0.15 (0.21)	—	1.00	0.13 (0.06–0.02)	0.15 (0.11)	—	1.00
T1	0.08 (0.04–0.21)	0.13 (0.12)	1.00	0.08 (0.03–0.24)	0.23 (0.30)	0.56	0.71	0.10 (0.05–0.26)	0.16 (0.13)	1.00	1.00
T8	0.07 (0.04–0.27)	0.15 (0.14)	1.00	0.10 (0.06–0.37)	0.25 (0.31)	0.032*	0.52	0.10 (0.06–0.22)	0.15 (0.12)	1.00	1.00
T16	0.10 (0.02–0.28)	0.15 (0.14)	1.00	0.10 (0.03–0.37)	0.27 (0.37)	0.09	0.64	0.10 (0.06–0.37)	0.20 (0.16)	1.00	0.84
T24	0.12 (0.03–0.22)	0.13 (0.12)	1.00	0.15 (0.07–0.31)	0.29 (0.37)	<0.001*	0.13	0.17 (0.11–0.35)	0.21 (0.14)	0.21	0.35
T36	0.16 (0.00–0.26)	0.15 (0.14)	1.00	0.11 (0.05–0.33)	0.29 (0.37)	0.002*	0.21	0.17 (0.11–0.41)	0.23 (0.18)	0.019*	0.21
T48	0.06 (0.03–0.23)	0.14 (0.14)	1.00	0.11 (0.03–0.34)	0.22 (0.28)	0.58	0.65	0.19 (0.12–0.31)	0.21 (0.14)	0.08	0.26
T60	0.06 (0.01–0.21)	0.14 (0.16)	1.00	0.14 (0.05–0.34)	0.27 (0.42)	0.02*	0.21	0.20 (0.10–0.47)	0.24 (0.19)	0.035*	0.15
SWSF, ml/min											
T0	0.25 (0.15–0.73)	0.48 (0.46)	—	0.22 (0.07–0.61)	0.35 (0.40)	—	0.592	0.38 (0.13–0.75)	0.50 (0.43)	—	1.00
T1	0.18 (0.11–0.74)	0.43 (0.44)	1.00	0.29 (0.07–0.54)	0.39 (0.42)	1.00	1.00	0.39 (0.21–0.65)	0.48 (0.31)	1.00	0.90
T8	0.22 (0.16–0.71)	0.46 (0.39)	1.00	0.29 (0.07–0.53)	0.42 (0.47)	1.00	1.00	0.61 (0.23–0.77)	0.59 (0.39)	0.254	0.68
T16	0.24 (0.10–0.56)	0.38 (0.39)	0.470	0.28 (0.06–0.57)	0.45 (0.50)	0.239	1.00	0.64 (0.33–1.06)	0.74 (0.51)	0.001*	0.07
T24	0.25 (0.11–0.67)	0.41 (0.38)	0.840	0.28 (0.06–0.7)	0.47 (0.50)	0.185	1.00	0.7 (0.26–0.83)	0.65 (0.41)	0.029*	0.18
T36	0.20 (0.08–0.67)	0.39 (0.39)	0.262	0.28 (0.07–0.72)	0.51 (0.55)	0.02*	0.97	0.66 (0.33–0.82)	0.66 (0.41)	0.007*	0.09
T48	0.20 (0.11–0.70)	0.39 (0.40)	0.278	0.23 (0.04–0.85)	0.43 (0.45)	1.00	1.00	0.74 (0.29–0.85)	0.67 (0.41)	0.004*	0.08
T60	0.25 (0.11–0.73)	0.35 (0.31)	0.077	0.24 (0.05–0.69)	0.40 (0.44)	1.00	1.00	0.59 (0.32–0.66)	0.61 (0.40)	0.087	0.12
SPF, ml/min											
T0	0.17 (0.00–0.47)	0.20 (0.21)	—	0.10 (0–0.2)	0.17 (0.25)	—	—	0.10 (0.02–0.4)	0.20 (0.21)	—	—
T1	0.05 (0.00–0.65)	0.36 (0.47)	1.00	0.01 (0–0.22)	0.14 (0.22)	1.00	—	0.10 (0.01–0.22)	0.17 (0.20)	1.00	—
T8	0.13 (0.00–0.41)	0.23 (0.28)	1.00	0.08 (0–0.24)	0.16 (0.23)	1.00	—	0.16 (0.06–0.35)	0.22 (0.24)	1.00	—
T16	0.06 (0.00–0.66)	0.28 (0.36)	1.00	0.06 (0–0.19)	0.17 (0.27)	1.00	—	0.23 (0.05–0.4)	0.26 (0.24)	1.000	—
T24	0.06 (0.00–0.26)	0.15 (0.16)	1.00	0.00 (0–0.43)	0.17 (0.28)	1.00	—	0.32 (0.18–0.55)	0.36 (0.28)	0.044*	—
T36	0.11 (0.00–0.36)	0.20 (0.24)	1.00	0.14 (0–0.4)	0.24 (0.27)	1.00	—	0.21 (0.12–0.33)	0.29 (0.33)	0.980	—
T48	0.10 (0.00–0.52)	0.26 (0.32)	1.00	0.15 (0–0.52)	0.35 (0.39)	0.656	—	0.29 (0.11–0.52)	0.32 (0.25)	0.107	—
T60	0.09 (0.00–0.26)	0.25 (0.46)	1.00	0.06 (0–0.38)	0.20 (0.29)	1.00	—	0.25 (0.03–0.47)	0.28 (0.23)	0.706	—
	Mean (S.D.)	**95% CI**	***P*-value (compared to baseline)**	**Mean** (S.D.)	**95% CI**	***P*-value (compared to baseline)**	***P*-value (compared to control)**	**Mean** (S.D.)	**95% CI**	***P*-value (compared to baseline)**	***P*-value (compared to control)**
CODS											
T0	3 (1.20)	2.34, 3.66	—	2.93 (1.28)	2.23, 3.64	—	—	2.40 (0.99)	1.85, 2.95	—	—
T1	2.67 (1.05)	2.09, 3.25	1.000	1.67 (1.50)	0.84, 2.50	0.005*	—	1.33 (0.90)	0.84, 1.83	0.03*	—

(continued)

Table 2 Continued

	Control group			Saline group				Saline/TA group			
	Median (IQR)	Mean (s.d.)	*P*-value (compared to baseline)	Median (IQR)	Mean (s.d.)	*P*-value (compared to baseline)	*P*-value (compared to control)	Median (IQR)	Mean (s.d.)	*P*-value (compared to baseline)	*P*-value (compared to control)
T8	2.93 (1.44)	2.14, 3.73	1.000	2.07 (1.58)	1.19, 2.94	0.140	—	1.80 (1.26)	1.10, 2.50	0.745	—
T16	2.33 (1.40)	1.56, 3.11	0.511	2.27 (1.33)	1.53, 3.01	0.511	—	1.20 (1.15)	0.57, 1.84	0.009*	—
T24	2.60 (1.55)	1.74, 3.46	1.000	1.87 (1.36)	1.12, 2.62	0.03*	—	1.07 (0.88)	0.58, 1.56	0.003*	—
T36	2.40 (1.40)	1.62, 3.18	0.745	1.73 (1.44)	0.94, 2.53	0.009*	—	1.40 (1.06)	0.82, 1.99	0.052	—
T48	2.40 (1.72)	1.45, 3.36	0.745	1.80 (1.47)	0.98, 2.62	0.017*	—	1.07 (1.28)	0.36, 1.79	0.003*	—
T60	2.40 (1.76)	1.43, 3.38	0.745	1.29 (1.38)	0.49, 2.08	<0.001*	—	0.87 (0.92)	0.36, 1.37	<0.001*	—
XI											
T0	46.3 (5.7)	43.2, 49.5	—	43.3 (5.3)	40.4, 46.2	—	0.49	42.6 (7.6)	38.4, 46.8	—	0.30
T1	46.2 (6.2)	42.8, 49.6	1.00	40.6 (6.6)	36.9, 44.2	0.240	0.07	41.8 (7.8)	37.5, 46.1	1.00	0.18
T8	44.8 (5.6)	41.7, 47.9	1.00	40.4 (7.2)	36.4, 22.4	0.162	0.18	39.8 (7.2)	35.8, 43.8	0.211	0.11
T16	46.3 (5.8)	43.1, 49.6	1.00	38.7 (8.6)	34, 43.5	0.003*	0.008*	39.5 (8.7)	34.7, 44.4	0.123	0.020*
T24	46.2 (5.9)	43.0, 49.4	1.00	38.1 (7.6)	33.9, 42.3	<0.001*	0.005*	40.0 (8.9)	35.1, 44.9	0.307	0.037*
T36	46.2 (6.3)	42.7, 49.7	1.00	37.1 (6.1)	33.7, 40.5	<0.001*	0.001*	39.6 (9.2)	34.5, 44.7	0.142	0.025*
T48	47.3 (6.1)	43.9, 50.6	1.00	38.1 (5.9)	35.4, 41	<0.001*	0.001*	39.3 (8.7)	34.5, 44.1	0.081	0.006*
T60	47.1 (5.7)	44.0, 50.2	1.00	39.6 (6.1)	36.2, 43	0.028*	0.009*	38.9 (8.2)	34.4, 43.5	0.032*	0.004*
ESSPRI											
T0	22.0 (5.1)	19.2, 24.8	—	17.7 (3.7)	15.6, 19.7	—	—	19.3 (5.0)	16.6, 22.1	—	—
T1	22.5 (5.3)	19.5, 25.4	—	17.3 (4.8)	14.7, 20.0	—	—	18.1 (6.4)	14.6, 21.7	—	—
T8	22.7 (3.8)	20.6, 24.8	—	15.9 (4.9)	13.2, 18.6	—	—	17.0 (6.0)	13.7, 20.3	—	—
T16	23.4 (3.7)	21.3, 25.4	—	18.1 (6.2)	14.7, 21.5	—	—	16.4 (6.5)	12.8, 20.0	—	—
T24	21.9 (5.2)	19.0, 24.7	—	17.7 (5.0)	15.0, 20.5	—	—	17.1 (7.3)	13.1, 21.2	—	—
T36	22.4 (5.1)	19.6, 25.2	—	16.1 (5.4)	13.2, 19.1	—	—	17.5 (7.1)	13.6, 21.5	—	—
T48	20.8 (7.0)	16.9, 24.7	—	17.1 (4.4)	14.7, 19.6	—	—	17.7 (5.3)	14.8, 20.7	—	—
T60	22.1 (6.7)	18.5, 25.8	—	18.4 (4.9)	15.7, 21.1	—	—	16.7 (5.7)	13.6, 19.9	—	—
Dryness domain of ESSPRI											
T0	8.0 (1.1)	7.3, 8.6	—	6.8 (1.7)	5.9, 7.7	—	0.13	7.9 (1.6)	7.0, 8.8	—	1.00
T1	7.9 (1.6)	7.0, 8.7	1.00	6.3 (2.0)	5.2, 7.4	1.00	0.03*	7.2 (2.2)	6.0, 8.4	1.000	0.61
T8	8.2 (1.1)	7.6, 8.8	1.00	5.7 (2.0)	4.5, 6.8	0.093	<0.001*	5.9 (1.9)	4.8, 6.9	<0.001*	0.001*
T16	8.5 (1.2)	7.9, 9.3	1.00	6.2 (2.2)	5.0, 7.4	1.00	0.001*	6.3 (2.0)	5.2, 7.4	0.004*	0.001*
T24	8.1 (1.5)	7.2, 8.9	1.00	6.3 (1.9)	5.2, 7.3	1.00	0.013*	6.1 (2.4)	4.7, 7.4	0.001*	0.005*
T36	8.1 (1.3)	7.4, 8.9	1.00	5.8 (2.3)	4.5, 7.1	0.201	0.001*	6.5 (2.0)	5.4, 7.7	0.025*	0.03*
T48	8.2 (1.3)	7.5, 8.9	1.00	6.3 (1.8)	5.3, 7.4	1.00	0.01*	6.7 (1.4)	5.9, 7.4	0.061	0.04*
T60	8.5 (1.4)	7.8, 9.2	1.00	6.7 (2.0)	5.6, 7.8	1.00	0.013*	6.1 (1.9)	5.1, 7.2	0.001*	0.001*

Data are median (interquartile range; IQR) and mean (s.d.) for UWSF, SWSF and SPF, and mean (s.d.) and 95%CI for CODS, XI and ESSPRI scores (total score and dryness domain) for all groups and time points. Bonferroni correction has been applied to *P*-values. *Significant. CODS: Clinical Oral Dryness Score; ESSPRI: EULAR SS Patient Reported Index; SPF: citric acid-stimulated parotid flow; SWSF: chewing-stimulated whole saliva flow; T0: 1 week before intervention; T1, T8, T16, T24, T36, T48, T60: 1, 8, 16, 24, 36, 48 and 60 weeks after sialendoscopy, respectively; UWSF: unstimulated whole saliva flow; XI: Xerostomia Inventory.

0.26, 2.27, $P = 0.005$) points between T1 and T0. Mean CODS score at T60 was 1.64 (95% CI: 0.54, 2.59, $P < 0.001$) points lower than T0. In addition, significant decreases compared with baseline were found at T24, T36 and T48. After sialendoscopy, XI decreased up to T36 but increased again from T48 onwards but remained lower than baseline. Mean XI differed significantly between time points [$F(7,294) = 4.700$, $P < 0.001$]. *Post hoc* tests revealed that mean XI at T16 was 4.60 (95% CI: 1.12, 8.08, $P = 0.003$) points lower compared with T0. At T60 mean XI was 3.73 (95% CI: 0.25, 7.21, $P = 0.03$) points lower compared with T0. In addition, significant differences compared with baseline were found for T24, T36 and T48 with a maximum difference of 6.27 (95% CI: 2.78, 9.45, $P < 0.001$) reached at T36.

No significant within-group differences were found for SWSF, SPF and the dryness domain of ESSPRI score ($P = 0.08$, $P = 0.24$ and $P = 0.17$, respectively).

Within-group analyses: saline/TA group

From T16 and onwards, UWSF increased compared with T0, and UWSF scores differed significantly between time points [$F(7,249) = 3.651$, $P = 0.001$]. *Post hoc* tests showed UWSF to be significantly increased at T36 compared with T0 (median: 0.17 *vs* 0.13 ml/min, $P = 0.019$). Also at 60 weeks UWSF (median: 0.20 ml/min) was still higher compared with T0 ($P = 0.035$).

Also SWSF scores improved over time and differed between time points [$F(7,294) = 4.125$, $P < 0.001$]. *Post hoc* tests showed SWSF to be increased at T16 compared with T0 (median: 0.64 *vs* 0.38 ml/min, $P = 0.001$). Differences remained significant up to and including T48.

From T8 onwards SPF values increased but decreased at T60, although remaining at a higher level compared with baseline. SPF differed between time points [$F(7,294) = 2.53$, $P = 0.015$]. *Post hoc* tests only showed the mean flow at T24 to be increased compared with T0 (median: 0.32 *vs* 0.10 ml/min, $P = 0.044$).

CODS decreased after intervention indicating an improvement in clinical signs of oral dryness. Mean CODS differed significantly between time points [$F(7,293) = 3.559$, $P = 0.001$]. *Post hoc* tests showed mean CODS at 1 week to be 1.07 (95% CI: 0.06, 2.07, $P = 0.03$) points lower than at T0. At 60 weeks mean CODS was 1.53 (95% CI: 0.53, 2.54, $P < 0.001$) points lower than at T0. In addition, mean CODS at T16, T24 and T48 were found to differ significantly from T0.

The dryness domain of the ESSPRI was lower compared with baseline from T8 onwards and the mean dryness domain of ESSPRI differed significantly between time points [$F(7,294) = 4.309$, $P < 0.001$]. *Post hoc* tests showed mean ESSPRI at T8 to be 2.00 (95% CI: 0.77, 3.23, $P < 0.001$) points lower than at T0. At 60 weeks mean ESSPRI was 1.80 (95% CI: 0.50, 2.97, $P = 0.001$) points lower than at T0. In addition, mean ESSPRI at T12, T16, T24 and 36 was found to differ significantly from T0. No significant within-group differences were found for XI [$F(7,294) = 2.022$, $P = 0.052$].

Discussion

The results of our study using subjective and objective measures indicate that sialendoscopy can result in an improvement of salivary flow and a reduction in the perceived oral dryness.

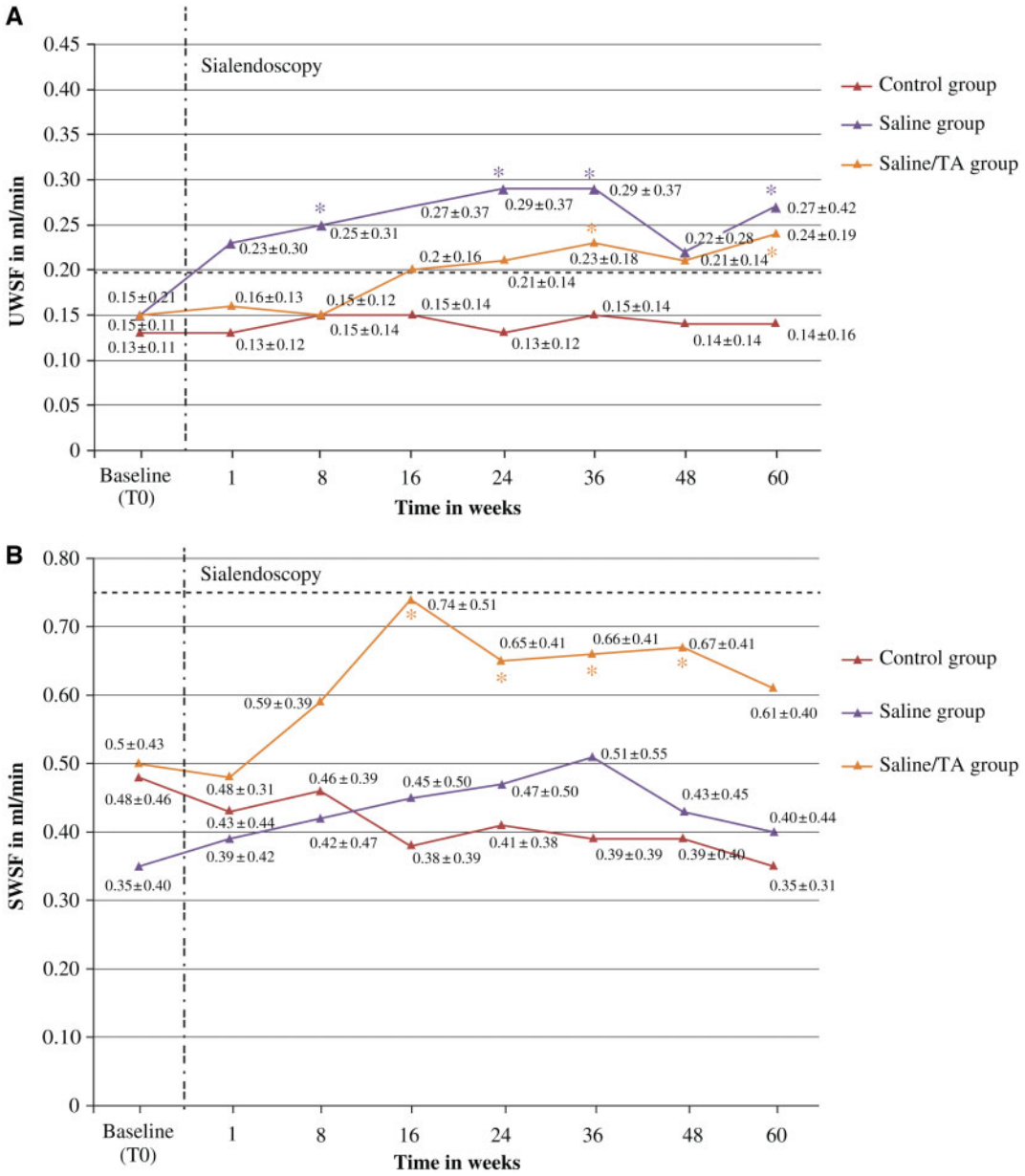
The increase in salivary secretion can be explained by dilatation prior to and during the endoscopic procedure as this may open ductal strictures and remove debris such as microsialoliths and mucus plugs [25]. In patients with SS and other autoimmune diseases, stricture formation is a frequent cause of salivary duct obstruction and recurrent sialadenitis [7, 26]. In our study, strictures were present and removed in all ducts that could be accessed. Additionally, Aframian *et al.* [27] suggest further mechanisms that may explain any beneficial effect of ductal irrigation that can also be applicable for sialendoscopic treatments [27]. For example, dilatation may induce stress conditioning. Based on animal models, it is suggested that exposure of salivary glands to injuries results in the propagation of salivary gland stem cell capabilities due to cellular plasticity in the glands' parenchyma. This could promote salivary gland repair [27–30].

Sialendoscopy might have greater efficacy in patients who have higher baseline salivary flow levels. It could be speculated that the greater effect of irrigation with saline/TA on the median SWSF is related to a higher median baseline SWSF level compared with that of the saline group. This could not be shown in our study as there was no significant difference at baseline between the groups. Furthermore, when we divided the participants into responders and non-responders and subsequently compared the baseline median UWSF and SWSF values of the responders and non-responders, no statistically significant differences were found. Additionally, disease stage could have a significant effect on treatment outcome. Patients with recent SS onset and more residual salivary gland capacity may benefit more from a sialendoscopic procedure, compared with patients with longer-term disease. Disease duration in the saline group was shorter than in the saline/TA group (8.1 and 11.1 years, respectively, Table 1) but no significant effect of disease duration on salivary secretion could be found.

The ductal system could be an effective route to deliver medications to affected glandular tissue and the tissues surrounding the ducts. Specifically, as the site of inflammation is located directly periductal, it could be speculated that a localized, ductal approach could be more effective than a systemic one. However, during the relatively short irrigation process, it is unclear how much TA is taken up by these tissues. An additional effect of saline combined with TA compared with saline alone is not fully supported by our findings.

A limitation of this study was that, in some patients, the sialendoscope could not be inserted because the papilla could not be identified or dilated, especially Wharton's ducts of patients in the saline/TA group. It is

FIG. 2 Mean UWSF and SWSF before and after sialendoscopic rinsing



The mean and standard deviations are reported for each time point. An UWSF of ≥0.2 ml/min and a SWSF of ≥0.75 ml/min are regarded as a "normal" salivary flow and are marked with a horizontal dashed line. Significant improvements compared with baseline (T0) are marked with asterisks ($P < 0.05$). SWSF: chewing-stimulated whole saliva flow; TA: triamcinolone acetonide; UWSF: unstimulated whole saliva flow.

known that sialendoscopy is more complicated to perform in submandibular glands than in parotid glands [31, 32]. This inconsistency could have introduced additional variation. Only 36.7% (11 of 30 ducts) of Wharton's ducts were accessible in the saline/TA group compared with 56.7% (17 of 30 ducts) in the saline group. In our study this was reflected in the *mean* (but not the *median*) UWSF as *mean* UWSF improved more in the saline group compared with the saline/TA group. For future studies a careful preoperative selection of patients will likely contribute to more predictable results and higher percentages of successfully irrigated glands. Additionally, surgically creating a new opening for inaccessible ducts could be tried.

We used a per-protocol analysis and therefore only data from participants who actually underwent the intervention and with complete follow-up were analysed. In literature it is argued that an intention-to-treat analysis is preferable for a randomized trial [33]. On the other hand, it is also argued

that a per-protocol analysis is preferable for trials with a one-time baseline intervention, such as ours, because intention-to-treat effects are agnostic about post-randomization decisions, including treatment refusal. An intention-to-treat analysis would reduce our intervention's effect if participants assigned to one of the intervention groups refused or were not able to undergo the planned intervention after randomization [34]. Therefore, we decided to use a per-protocol analysis beforehand. With regard to follow-up, we do not expect a large difference in outcomes between an intention-to-treat analysis and a per-protocol analysis because of the low number of withdrawals and the reasons for withdrawal in our study. Participants were lost during follow-up because of reasons not related to the intervention or its consequences. Furthermore, the sample size was not significantly reduced and therefore there was no reduction in study power.

In future studies, the effect of retreatments and, when shown effective, the optimal retreatment interval should be assessed. Furthermore, treatment of multiple salivary glands in the same session could be performed under local anaesthesia, as in literature it is suggested that this is possible and safe [35, 36]. Treatment under local anaesthesia makes retreatments also more feasible.

Sialendoscopic intervention had a significant effect on perceived oral dryness. This could be related to an increased flow, but also to a change in saliva protein composition such as an increased MUC5b concentration [8, 37]. This improvement in perceived oral dryness could also be due to a placebo effect as it was not possible to perform the study as a double-blind randomized trial. But this perceived oral dryness improvement is supported by an increase in salivary secretion.

There is emerging evidence that Sjögren's syndrome patients could benefit from sialoendoscopy of the salivary gland ductal system. Endoscopic irrigation might evolve into a treatment option that might improve salivary gland functioning and thus reduce xerostomia complaints in patients who are diagnosed with Sjogren's syndrome and xerostomia complaints, and have a remaining salivary flow.

Conclusion

Salivary endoscopy of SS patients increases salivation and reduces oral dryness up to at least 60 weeks after sialendoscopy.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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