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Improvement of dry mouth following intraductal irrigation of salivary glands

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Abstract

Objectives: To assess the effect of major salivary gland intraductal irrigations (IGs) to relieve mouth dryness.

Methods: We retrospectively analyzed the records of patients with mouth dryness who underwent major salivary gland IG during 2013–2015. Records included demographics, medical background, dry mouth etiologies and symptomatology, and results of sialometry and sialo-cone-beam computerized tomography. Subjective improvement following the IG procedure (yes/no) and sustained subjective improvement (mouth dryness relief for ≥1 month) were recorded. Objective improvement was assessed by comparing the mean unstimulated (USF) and stimulated (SSF) whole salivary flow (WSF) rate before and after the IG.

Results: Seventy-four patients were included [mean age: 59.08 ± 12.46 years]. Improvement was detected in the USF (p = .027), but not in the SSF (p = .878). Fifty-five (84.6%) noted subjective improvement, while 10 (15.4%) did not. Subjective improvement was positively associated with the USF following IG (p = .037), with salivary gland swelling episodes (p = .033), and with difficulties in swallowing dry foods (p = .014). Of those with subjective improvement, 45 (81.8%) reported sustained improvement, which was positively associated with lack of a gritty eye sensation (p = .042) and abnormal sialo-CBCT findings (p = .001).

Conclusions: Major salivary gland IG is a simple and safe procedure that may relieve dry mouth for a relatively extended duration. Further studies are needed to confirm these preliminary findings and assess their underlying mechanisms.

KEYWORDS

dry mouth, intraductal salivary irrigation, medication-induced salivary gland dysfunction, saliva, salivary flow, salivary glands

1 | INTRODUCTION

Saliva is considered as the *aqua vita* of the oral cavity with multiple functions. It includes antibacterial, antiviral, and antifungal ingredients and serves as a source for biological components that act against tooth abrasion, attrition, erosion, and dental caries (Dawes et al., 2015). Saliva has moistening and lubrication capabilities, and it assists in dissolving solid tastants and contains digestive enzymes (Dawes et al., 2015).

The average overall secretion capacity of healthy salivary glands is estimated to be around 0.6 liters a day (Watanabe & Dawes, 1988). Mouth dryness is a common morbidity that encompasses both a subjective feeling termed xerostomia and an objective measurement of reduced saliva, termed hyposalivation.

Interestingly, no direct correlation is observed between xerostomia and hyposalivation, unless more than 50% in salivary flow is diminished (Ship, Fox, & Baum, 1991; Sreebny & Vissink, 2010). The prevalence of xerostomia increases with age reaching ~30% of the population aged 65 and older (Ship, Pillemer, & Baum, 2002). The major etiologies for mouth dryness are medication-induced salivary gland dysfunction (MISGD) (Dawes et al., 2015), Sjögren's syndrome (Aframian, Konttinen, Carrozzo, & Tzioufas, 2013), radiation damage to the salivary glands (Siddiqui & Movsas, 2017), and other conditions including uncontrolled diabetes mellitus and renal diseases. Dry mouth disrupts the normal homeostasis of the oral cavity, and therefore, people with dry mouth are more prone to develop oral candidiasis, dental caries, taste disorders, and difficulties in speech, chewing, and swallowing (Ouanounou, 2016).

At present, available treatment modalities for mouth dryness include the following: altering the intake of xerogenic medication when possible; shifting the radiation field to protect the salivary glands in head and neck cancer patients [i.e., intensity-modulated radiation therapy (IMRT)] (Wang & Eisbruch, 2016); local application of saliva substitutes and stimulants; systemic intake of muscarinic agonists (sialogogues), such as pilocarpine and cevimeline (Aframian, Helcer, Livni, & Markitziu, 2006; Mercadante, Al Hamad, Lodi, Porter, & Fedele, 2017); and electrostimulation devices (Wolff et al., 2018). Since the prevalence of salivary gland impairment is relatively common (Ship et al., 2002), more cost-effective modalities are needed to overcome this morbidity.

Previously, it was shown that major salivary intraductal irrigation (IG) is a safe, simple, and effective treatment option for patients with obstructive and inflammatory diseases that cause the development of mucus plugs, strictures, or stenosis (Antoniades, Harrison, Epivatianos, & Papanayotou, 2004; Lee et al., 2017). Our hypothesis in this study was that IG will help to provide relief of dry mouth in cases of impaired major salivary gland function and, consequently, will offer another non-pharmacological treatment modality for this large patient population. Therefore, our primary goal was to assess the subjective and objective improvements in mouth dryness following major salivary gland intraductal irrigations (IGs).

2 | SUBJECTS AND METHODS

2.1 | Study design

This study retrospectively analyzed the medical records of all patients suffering from mouth dryness who underwent major salivary gland IG procedures at the Salivary Glands Clinic, Hebrew University-Hadassah Hospital, between January 1, 2013, and December 31, 2015, and met the inclusion and exclusion criteria. This clinic is a secondary specialist center that manages the treatment of salivary gland pathologies referred by dentists and physicians. All irrigations were performed by a single operator (DJA).

2.2 | Ethical approval

The study adhered to STROBE guidelines and met the requirements of the Hadassah Medical Organization's (HMO) Institutional Review Board (IRB) (No. 0489-15-HMO, date of approval: 10.09.2015). Since this study was retrospective and involved only medical record analysis, the IRB approved exemption from informed consent.

2.3 | Inclusion and exclusion criteria and diagnoses

Inclusion criteria: patients who underwent salivary IG procedures, aged 18–90 years.

Exclusion criteria: any individuals with a history of drug/alcohol/medication abuse; patients with medical and/or dental emergencies; patients who were pregnant or lactating; individuals with acute sialadenitis, the presence of silaloliths, and/or a complete stricture of the duct orifices; and anyone with no records regarding sialometry tests before the initial IG and after the last IG.

2.4 | Data collection

According to the routine protocol of the Salivary Glands Clinic, all patients were evaluated at their first visit to the clinic, before the IG procedure, using a guided face-to-face, detailed questionnaire followed by a clinical examination and unstimulated (USF) and stimulated (SSF; 2% citric acid) whole salivary flow (WSF) measurements. Sialometry tests were performed after 2 hr without food intake, mouthwash use, or toothbrushing and without sialogogue intake at the day of the salivary flow measurement. USF and SSF were collected using the spitting method for 10 min as described previously (Navazesh, 1993). The time of day for saliva collection was standardized for each subject as for original reference (Navazesh, 1993).

The IG procedure for the patients with dry mouth included the four major salivary glands (i.e., bilateral parotid and bilateral submandibular). In cases of obstruction of one or more of the salivary glands orifices, the IG was performed in the remaining available open salivary glands. Orifice exploration was obtained with sterile lacrimal probes (RZ Medizintechnik GmbH). Prior to insertion, the probe tips were dipped with lidocaine gel (Rafa Laboratories). Probe tips were inserted to the orifices of Wharton's and/or Stensen's ducts and used for duct dilation, starting with #0000 (0.45 mm diameter) or #000 (0.5 mm diameter), respectively, and gradually increased to #1 diameter probes (1.1 mm diameter). Thereafter, IG was obtained by gradually filling the glands with 3 ml of a sterile saline solution using a 24- or 22-gauge cannula for the Stensen's

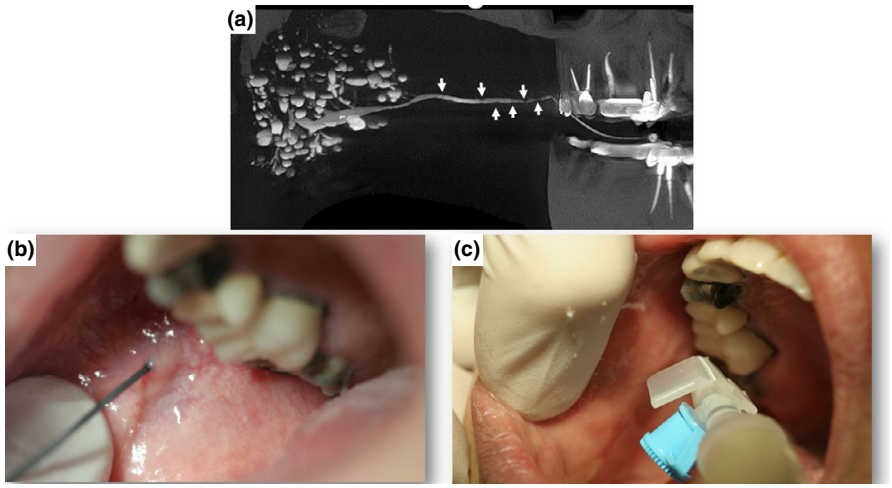

FIGURE 1 IG method to the right parotid gland. A: Cone-beam computerized tomography sialography of parotid gland in Sjögren's syndrome patient showing typical features of sialectasis as well as irregular ductal morphology with multiple strictures along the Stensen ducts (arrows). B: Insertion and dilatation with a lacrimal probe. C: IG with saline using a 24-gauge cannula [Colour figure can be viewed at wileyonlinelibrary.com]

and Wharton's ducts, respectively (Figure 1). Immediately after the filling process, the gland area was massaged to discharge the residual saline into the oral cavity. In this study, IGs were performed on the following salivary glands: unilateral parotid, bilateral parotid, and bilateral submandibular, bilateral parotid, and submandibular glands.

The IG was repeated after ~6 months. Following the IG procedures, patients were monitored and were asked whether their condition improved (yes/no question). Subjective improvement was defined as mouth dryness relief in a nominal scale: yes/no. Sustained subjective improvement was defined as mouth dryness relief for ≥1 month after the last irrigation.

Objective change in salivary gland flow was assessed by comparing the mean USF and SSF sialometry results after the last IG procedure with those obtained before the IG procedure.

The records included the following information:

1. Demographic details: age; and sex (male/female).
2. Smoking habits: current smoking (yes/no).
3. Consumed liquids by the patient in milliliters per day according to the patient's estimate.
4. Medical background: The diagnosis of systemic conditions was based on the reported medical history as well as on a written medical information form, supplied by the family physician of the patient. The medical information form included medical diagnoses and medications taken by the patient. Medical status was categorized according to the American Society of Anesthesiologists (ASA) classification (Fitz-Henry, 2011) as follows: healthy (ASA I) and not healthy (ASA II + ASA III).
5. The total number of medications taken by the patient, as well as the consumption of xerogenic medications.
6. Salivary flow manipulators were recorded, as follows:
   a Systemic sialogogues, that is, use of pilocarpine or cevimeline (yes/no).
   b Salivary flow local manipulators included the use of one or more of the following: mouthwashes, lubrication gels, oral sprays, sucking non-sugarless candies, and/or gum chewing (yes/no).
7. Etiologies for dry mouth of the patients who underwent salivary gland IG included the following:
   a Iatrogenic causes: medication-induced salivary gland dysfunction (MISGD), radiation-induced hyposalivation, and radioactive iodine-induced hyposalivation.
   b Autoimmune cause: primary or secondary Sjögren's syndrome.
   cMiscellaneous, including chronic sialadenitis, sialadenosis (sialosis), idiopathic causes, and other causes.
8. Self-reported signs and symptoms related to salivary gland impairment included the following:
   a Difficulty in swallowing dry foods (yes/no).
   b Dry eye symptoms and/or gritty feeling in the eye (yes/no).
   cHistory of salivary gland swelling episodes (yes/no).
9. Results of cone-beam computerized tomography sialography (sialo-CBCT) evaluating the salivary glands, as either within normal limits or having at least one abnormal finding.

2.5 | Statistical analysis

SPSS software version 22.0 was used to perform statistical analysis of the data. Two-tailed statistical significance (α) level was defined as $p < .05$. Continuous variables are displayed as means and standard deviations, while categorical variables are displayed as frequencies and percentages.

Sialometry results before IG and after the last IG were analyzed with the non-parametric Wilcoxon test. Associations between subjective improvement and categorical independent variables were analyzed with Fisher's exact test, and associations between subjective improvement and continuous variables were analyzed with an independent *t* test or a non-parametric Mann–Whitney test. Associations between subjective improvement (yes/no) and the USF as well as the SSF, before and after salivary IGs, were analyzed with a non-parametric Mann–Whitney test.

TABLE 1 Demographic and medical characteristics of patients undergoing salivary intraductal irrigations (IGs) (*N* = 74)

Parameter	Parameter	Value
Sex (*N* = 74)	Male	21 (28.4%)
	Female	53 (71.6%)
Medical status	Healthy (ASA I)	6 (8%)
	Not healthy (ASA II + III)	68 (92%)
Smoking (*N* = 71)	No	59 (83.1%)
	Yes	12 (16.9%)
Systemic medications (*N* = 73)	Yes	64 (87.7%)
	No	9 (12.3%)
Medication-induced salivary gland dysfunction (*N* = 69)	Yes	43 (62.3%)
	No	26 (37.7%)
Salivary flow manipulators	Systemic sialogogues	36 (48.6%)
	Local salivary flow manipulators	20 (27.0%)
	None	18 (24.3%)

Parameter	Mean ± *SD*	Median	IQR	Min–Max
Age	59.0 ± 12.4	62	50.7–68.0	29–83
Number of medications	3.2 ± 2.1	3	2–4	0–10
Consumed liquids per day (ml)	1691 ± 693	1,600	1250–2000	400–4000

Abbreviations: IQR, interquartile range; Max, maximum; Min, minimum; MISGD, Medication-induced salivary gland dysfunction; ml, millilitres; *SD*, standard deviation.

3 | RESULTS

3.1 | General description

During the study period, a total of 157 patients attended the Salivary Glands Clinic; of those, 74 patients underwent salivary gland IG and met the inclusion and exclusion criteria. The IG procedure was not associated with any major adverse effects.

Table 1 presents the demographic and medical characteristics of the patients undergoing salivary IG. Most patients were not healthy, non-smokers, consumed systemic medications, and experienced MISGD. Systemic sialogogues and local salivary flow manipulators were used by most patients. The volume of liquids consumed by the patients (Table 1) was higher compared to the previously reported amount of 1575 milliliters per day in sedentary adults living in temperate climate (Jequier & Constant, 2010; Table 1).

Table 2 presents the diagnoses, auxiliary tests, and gland distribution of the irrigated salivary glands among the study population.

Table 3 presents the sialometry results prior to and after the last IG procedure of each patient. A statistically significant improvement was detected in the USF, but not in the SSF.

Figure 2 presents the subjective assessment of dryness by the study patients after the last IG procedure. Of the 65 patients who answered this question, most indicated that the IG procedures improved their condition; that is, they felt less dry. Moreover, of those who noted an improvement, most reported that the improvement was sustained (≥1 month).

Table 4 presents the parameters that were positively associated with subjective improvement (yes/no) after salivary gland IGs as well as with a sustained subjective improvement after salivary IGs (≥1 month) (Table 4). The diagnoses/etiologies for dry mouth were not associated with subjective improvement (likelihood ratio: $p = .703$).

Associations between subjective improvement and whole salivary flow (WSF) before and after the last salivary gland IG are also presented in Table 4. Subjective improvement was positively associated with the USF after the IG procedures.

Salivary flow rates after the IG procedures were statistically significantly lower in patients on systemic sialogogues compared to those who did not use sialogogues (USF: 1.4 ± 1.2 vs 3.5 ± 1.7, respectively, $p < .001$; and SSF: 1.9 ± 1.9 vs 4.5 ± 1.9, $p < .001$). Subjective improvement in oral dryness had no statistically significant association with sialogogue use (Fisher's exact test: $p = .270$).

The number of IG procedures had a slight positive association, which was close to statistical significance, with the subjective improvement ($p = .064$; Table 4). The type of irrigated glands was not associated with subjective improvement (likelihood ratio: $p = .591$) nor with the USF and SFF (non-parametric related-samples Kruskal–Wallis test: $p = .099$ and $p = .262$, respectively).

TABLE 2 Diagnoses, auxiliary tests, and type of salivary intraductal irrigation (IG) of the study population (*N* = 74)

Parameter		Variable		*N* (%)
Etiologies for dry mouth	Iatrogenic cause	Drug-induced hyposalivation		5 (6.8%)
		Radiation-induced hyposalivation		6 (8.1%)
		Radioactive iodine-induced hyposalivation		8 (10.8%)
	Autoimmune cause	Sjögren's syndrome		27 (36.5%)
	Miscellaneous cause	Chronic sialadenitis		12 (16.2%)
		Sialosis		8 (10.8%)
		Idiopathic		4 (5.4%)
		Other		4 (5.4%)
Sialo-cone-beam computerized tomography (CBCT)		Performed sialo-CBCT	Normal results	10 (13.5%)
			Abnormal results	43 (58.1%)
		Not performed		21 (28.4%)
Irrigated glands		Unilateral parotid		4 (5.4%)
		Bilateral parotid		50 (67.6%)
		Bilateral submandibular		2 (2.7%)
		Bilateral parotid+submandibular		18 (24.3%)

Parameter	Mean ± *SD*	Median	IQR	Min–Max
Number of irrigations	5.7 ± 4.7	4.0	2.0–8.25	1.0–25.0
Follow-up (weeks)	34.7 ± 28.9	27.0	12.75–52.0	2.0–128.0

Abbreviations: *SD*: standard deviation; IQR: interquartile range; Min: minimum; Max: maximum.

TABLE 3 Sialometry results before and after the last salivary intraductal irrigation (IG)

	Whole salivary flow before salivary IG				Whole salivary flow after the last salivary IG				
	Mean ± *SD*	Median	IQR	Min–Max	Mean ± *SD*	Median	IQR	Min–Max	*p* value*
Unstimulated whole salivary flow (ml/10 min)	1.89 ± 1.85	1.40	0.40–2.82	0–8	2.41 ± 2.43	1.55	0.4–3.9	0.0–12.0	**.027**
Stimulated whole salivary flow (ml/10 min)	2.97 ± 2.47	2.80	0.75–5.00	0.0–12.0	3.08 ± 2.92	2.40	0.6–4.7	0.0–12.0	.878

Abbreviations: IQR, interquartile range; Max, maximum; min, minutes; Min, minimum; ml, milliliters; *SD*, standard deviation; SSF, Stimulated whole salivary flow; USF, Unstimulated whole salivary flow.

Bold values represent statistically significant *p* values.
*Non-parametric related-samples signed-rank Wilcoxon test.

4 | DISCUSSION

Hyposalivation is a morbidity that harms oral mucosal and dental health and consequently impairs an individual's quality of life (Aliko et al., 2015). Although there are treatments available to relieve mouth dryness, no ideal agent is currently available to treat specific etiologies effectively, and consequently, there is still a need for other ones, because of its high prevalence, with many people unable to find adequate improvement (Ship et al., 2002; Turner, 2016). IG of the major salivary glands is an easy technique that is typically not accompanied by any significant adverse effects (Izumi et al., 1998; Lee et al., 2017). The main aim of the IG procedure is to open and clear any obstructions and strictures of the salivary ductal compartment in cases of chronic obstructive sialadenitis, recurrent juvenile parotitis, Sjögren's syndrome, and post-radioiodine treatment (Lee et al., 2017). Additionally, the IG procedure is less invasive than sialendoscopy (Karagozoglu et al., 2018). However, sialendoscopy enables the utilization of invasive tools for opening strictures, dilation using balloons, sialolithiasis removal, and stent insertion, as well as direct, real-time, live imaging of the intraductal space (Karagozoglu et al., 2018). Nevertheless, IG is a relatively simple procedure, which is cost-effective and has fewer complications (Lee et al., 2017). Moreover, it can be performed on both Wharton's ducts and both Stensen's ducts at the same visit. Furthermore, it does not require expensive equipment and special surgical qualification.

The present study demonstrated that IG can lead to both subjective self-reported improvement of xerostomia and objective

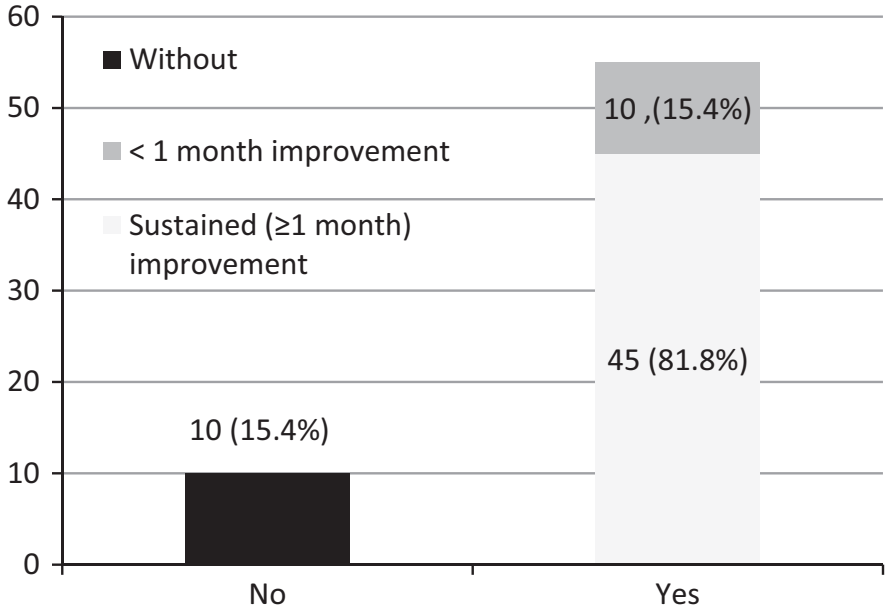

FIGURE 2 Subjective improvement following the last salivary intraductal irrigation (IG)

improvement in salivary flow. Importantly, the study demonstrated a relatively long-term relief (≥1 month) in xerostomia in most of the patients as well as a relatively long-lasting increase in USF rate (≥1 month).

4.1 | Effect of salivary IG on subjective improvement of dry mouth

Currently, patient-centered care and patient satisfaction are given increased emphasis in health care as valuable outcome measures (Kuipers, Cramm, & Nieboer, 2019). In the present study, subjective improvement following IG was positively associated with patients expressing fewer signs of hyposalivation at baseline, such as a lack of difficulty in swallowing dry foods and a lack of a gritty eye sensation. Fewer signs and symptoms may contribute to the likelihood of IG resulting in a better subjective improvement. It is also likely that less signs and symptoms means less damage to the salivary glands. Thus, this observation may will who those among discriminate the from most benefit IG procedure.

About a third of the patients were diagnosed with Sjögren's syndrome, and their general subjective improvement might account for their report of less gritty eye sensation. It should be noted, however, that the positive association between subjective improvement and gritty eye sensation could also be a result of common cause for both (confounding effect), other than the irrigation. Therefore, this subjective finding should be further explored in future studies using objective measurements such as Schirmer's test or the Rose Bengal test.

Abnormal findings in sialo-CBCT were also associated with sustained subjective improvement. The sialo-CBCT is known to have high resolution of details and therefore contributes to a correct diagnosis (Keshet, Aricha, Friedlander-Barenboim, Aframian, & Nadler, 2018). It is possible that the improvement following sialo-CBCT is due to its contribution to the correct diagnosis and, therefore, appropriate treatment. Additionally, it is possible that the actual procedure of sialo-CBCT acts as an IG and can help in situations where there is obstruction or stenosis (Brown, 2006). Indeed, previous reports demonstrated that among juvenile recurrent parotitis, the damaged parotid gland is capable of regeneration subsequent to the sialographic examination (Galili & Marmary, 1985).

Interestingly, salivary gland swelling history was positively associated with subjective improvement. We hypothesize that a recognizable change of less swelling episodes by patients following the salivary IG may account for their perception of subjective improvement. Future studies should test the validity of this hypothesis.

4.2 | Effect of salivary IG on USF vs SSF

While an increase in USF was observed, there was no statistical difference in the SSF. The long-term beneficial effect of the IG on USF may be related to the fact that the salivary glands are working in an unstimulated or resting state most of daily time (Sreebny & Vissink, 2010), with true stimulation only occurring during meals or other times of food/stimulant consumption.

Moreover, almost half of the patients were treated with systemic sialogogues, that is, the parasympathetic drugs that stimulate the salivary secretion pathway. Considering that, we hypothesize that this may have already activated the remaining acinar parenchyma to produce some residual saliva. Consequently, the IG procedure effect on SSF may have been negligible. Accordingly, the use of IGs may be particularly beneficial to relieve mouth dryness in cases where there are contraindications to using sialogogues. Supporting the hypothesis that the remaining acinar parenchyma could already have been activated by the use of systemic sialogogues is our finding of lower salivary flows achieved among patients on systemic sialogogues which were lower compared to those who did not use sialogogues.

TABLE 4 Associations of subjective improvement after the last salivary intraductal irrigation (IG) with various clinical parameters

Parameters		Subjective improvement after salivary IG irrigations: Yes *N* (%)	No *N* (%)	*p* Value*
History of salivary gland swelling episodes	Yes	23 (95.8%)	1 (4.2%)	**.033**
	No	22 (73.3%)	8 (26.7%)	
Difficulty in swallowing dry foods	Yes	8 (61.5%)	5 (38.5%)	**.014**
	No	31 (93.9%)	2 (6.1%)	

Parameters	Subjective improvement after salivary IG: Yes Mean ± *SD*	No Mean ± *SD*	*p* value**
Unstimulated whole salivary flow (USF) before the irrigations	1.86 ± 1.82	1.07 ± 1.27	.096
Stimulated whole salivary flow (USF) before the irrigations	3.21 ± 2.50	2.02 ± 2.22	.113
Unstimulated whole salivary flow (USF) after the irrigations	2.46 ± 2.50	1.19 ± 1.43	**.037**
Stimulated whole salivary flow (USF) after the irrigations	3.12 ± 2.98	1.79 ± 2.04	.105
Number of irrigations	6.62 ± 4.77	4.50 ± 4.64	.064

Parameters		Subjective improvement after salivary IG irrigations: ≤ 1 month	Sustained (>1 month)	*p* value*
Gritty eye sensation	Yes	12 (100.0%)	0 (0.0%)	**.042**
	No	10 (30.3%)	23 (69.7%)	
Sialo-cone-beam computerized tomography (CBCT)	Normal results	5 (62.5%)	3 (37.5%)	**.001**
	Abnormal results	1 (3.3%)	29 (96.7%)	

Bold values represent statistically significant *p* values.

**p*: Fisher's exact test.

***p*: non-parametric tests: independent-samples Mann–Whitney test.

4.3 | Long-term beneficial effect of salivary IG

The relief in subjective and objective dryness could be partially explained by the mechanical procedure that acts as a blockage removal, which theoretically could stimulate some reparative gland processes. Indeed, the dilatation prior to the IG may open ductal strictures and remove debris such as micro-sialoliths and mucus plugs (Lee et al., 2017). Additionally, in pathologies such Sjögren's syndrome, MISGD, and radiation-induced hyposalivation, glandular cells may experience obstructed signaling pathways for secretion and/or impaired vascularization. We suggest that there are further mechanisms that may explain any long-term beneficial effect; thus, the combination of dilatation together with retrograde IG as mechanical maneuver may induce stress conditioning. This hypothesis is based on previous animal models, which demonstrated that exposure of salivary glands to injuries, such as duct ligation (mechanical maneuver) or short heat stress conditioning, resulted in propagation of salivary gland stem cell capabilities due to cellular plasticity in the glands' parenchyma promoting salivary gland repair (David, Shai, Aframian, & Palmon, 2008; Okumura et al., 2003; Weng, Aure, Maruyama, & Ovitt, 2018).

It should be noted that representative of the everyday scenario in salivary gland clinics, the study population was composed of patients with different etiologies for dry mouth, and consequently, different underlying pathological mechanisms. For example, the largest group in this cohort was Sjögren's syndrome patients in whom the glands' impairment is caused by immune dysregulation processes mainly affecting the acinar compartment of the gland (Campos, Hillen, & Barone, 2016). Conversely, in the "radioactive iodine-induced" group, the main affected part is the luminal ductal cells, which contain the sodium/iodide symporters that account for increased accumulation of I-131 (Aframian et al., 2006; Van Nostrand, 2011). Interestingly, in this study, the diagnosis/etiologies for dry mouth had no statistically significant association with both subjective and objective improvements. Moreover, the number of IG procedures had only a slight positive association, which was close to statistical significance, with the subjective improvement. However, due to the heterogeneity and size of the study population, additional

longitudinal studies with larger number of patients with comparable diagnoses should explore the secondary outcomes of this study, as well as the underlying mechanisms that account for the observed subjective and objective improvements of dry mouth following salivary gland IG.

4.4 | Association between subjective and objective improvements

A positive association was found between the subjective improvement and the USF after the IG. This is in line with our hypothesis that the beneficial effect of salivary glands IG is beyond a placebo effect, and the subjective improvement could be, at least in part, attributed to improvement in the hyposalivation.

Limitations of the present study include the convenience cohort that might cause a selection bias and limit the generalizability of our results. However, patients were referred to the salivary gland clinic from all over the district. Furthermore, our preliminary results are before-and-after and the study lacks comparison group without the intervention.

Another limitation of the study is the use of a single-item question to assess the subjective symptom of dry mouth, which limits our ability to capture the severity and variability of xerostomia. This subjective finding should be further explored in future studies using multi-item approaches that will include either a battery of items and/or a summated rating scale such as the 11-item Xerostomia Inventory (Thomson, Chalmers, Spencer, & Williams, 1999; Ying Joanna & Thomson, 2015).

5 | CONCLUSION

Additional studies in different settings and populations and with more homogenous group stratification in the intervention group as well as a comparison group without the intervention are needed to confirm these preliminary findings and further assess the mechanisms underlying the beneficial effect of the IG procedure.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Doron J Aframian; Made substantial contributions to the study's conception and design, acquisition of data, and analysis and interpretation of data; drafted, revised and provided final approval of the version to be published. Sagit Baaton; Data collection, interpretation of the results, revised and approved the manuscript Sigal Mazor; Analysis and interpretation of data and approved the manuscript. Nadler Chen; Interpretation of the results revised and approved the manuscript. Naama Keshet; Interpretation of the results revised and approved the manuscript. Yaron Haviv; Interpretation of the results revised and approved the manuscript. Yehuda Zadik; Interpretation of the results revised and approved the manuscript. Rinat Schwimmer-Noy; Data collection, interpretation of the results, revised and approved the manuscript. Boaz Shay; revised and approved the manuscript. Galit Almoznino; Made substantial contributions to the study's conception and design, data collection, interpretation of data, drafted, revised and approved the manuscript and submitted the version to be published.

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