Intra-Operative Visualization and Treatment of Salivary Glands in Sjögren’s Syndrome by Contrast-Enhanced Ultrasound Sialendoscopy (CEUSS): Protocol for a Phase I Single-Center, Single-Arm, Exploratory Study.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON26628

Source
NTR

Brief title
CEUSS

Health condition

Sjögren's syndrome

Sponsors and support

Primary sponsor: Amsterdam UMC, VU Medical Center dep. of Oral and Maxillofacial Surgery and Oral Pathology
Source(s) of monetary or material Support: Amsterdam UMC, Location VU Medical Center, department of Oral and Maxillofacial Surgery

Intervention

Outcome measures

Primary outcome

Main outcomes will be an evaluation of the safety and practical applicability of the experimental treatment. Safety will be determined by unanticipated treatment-related mortality, and the occurrence of adverse events (AEs) and serious adverse events (SAEs). AEs will be defined as any undesirable experience occurring to a subject during the experimental treatment period, whether or not related to the investigational intervention. SAEs will be defined as any untoward medical occurrence or effect that, at any dose is life threatening (at the time of the event); requires hospitalization or prolongation of existing in-patients' hospitalization; results in persistent or significant disability or incapacity; or is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction. Practical applicability will be defined as accomplishment of the experimental protocol during the procedure.

Secondary outcome

Exploratory outcomes of CEUSS will include measurements of unstimulated whole mouth saliva flow (UWSF), stimulated whole mouth saliva flow (SWSF), stimulated parotid saliva flow (SPSF) and the clinical oral dryness score (CODS) [21,22]. Changes due to CEUSS in reported pain, mouthfeel and clinical SS symptoms will be determined in comparison to initial values using a set of validated questionnaires, i.e., the McGill Pain Questionnaire (MPQ), Xerostomia Inventory (XI), and European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI). Furthermore, changes in salivary cytokine profiles will be determined (IL-1β, IL-6, BAFF, IL-12, IL-18 and TNFα). Finally, salivary gland topographical alterations will be evaluated by US using the Hočevar score. The echostructure of the treated glands will be graded at T-4 (4 weeks before intervention), T1 (1 week after intervention) and T16 (16 weeks after intervention).

Study description

Background summary

We established a promising sialendoscopic treatment for in vivo enhancement of salivation in salivary glands affected by Sjögren's syndrome (SS). In this technique, the ducts of the salivary glands are irrigated with saline and steroids. This allows for dilatation of ductal strictures and removal of debris. Unfortunately, it is not possible to assess the delivery and penetration of saline or medications in the ductal system and parenchyma. To address this problem, we will conduct contrast-enhanced ultrasound (US) sialendoscopy (CEUSS) using sulphur hexafluoride microbubbles. To our knowledge, microbubbles have never been used

for the treatment of salivary glands in SS. It is, therefore, imperative to test this application for its safety and feasibility

A single-arm phase-I study will be performed in 10 SS patients. Under local anaesthesia, US-guided infusion of the parotid and submandibular glands with microbubbles will be performed. Continuous ultrasound imaging will be used to visualize the glands, including the location of strictures and occlusions.

To our knowledge, microbubbles have never been used for the treatment of obstructed salivary glands in patients affected by SS. It is, therefore, imperative to evaluate this new application for its feasibility and safety. The aim of this study is to assess the safety and practical applicability of CEUSS in the salivary glands of patients with SS. Practical applicability will be defined as accomplishment of the experimental protocol during the procedure. To evaluate functional outcomes, we will meticulously monitor for serious adverse events (SAEs) and assess whether changes in saliva flow, oral dryness indices, and subjective mouthfeel occur. This evaluation will be performed in a phase I, single-center, single-arm, exploratory study

Study objective

We hypothesize that CEUSS is a feasable and safe technique to use in large salivary glands affected by Sjögren's syndrome.

Study design

T-6 Inclusion/exclusion and informed consent (6-4 weeks before intervention)
During the first appointment it is verified whether a volunteer meets the inclusion criteria. The aim of the study will be explained and the volunteers receive the information for participants and the informed consent letter. Smoking habits and medication use are noted.

T-4 (4 weeks before intervention, baseline)
During this appointment volunteers can ask remaining questions regarding the study. Furthermore, the volunteer can decide whether they want to participate in the study. If the volunteer decides to participate, the informed consent letter will be signed, and unstimulated and stimulated whole mouth and stimulated parotid saliva (UWS/SWS/SPF) will be collected according to our published protocol (5). Briefly, UWS will be collected immediately after an initial swallow, and in 30 seconds intervals for 5 min. To collect SWS, patients will be asked to chew a 5×5 cm sheet of paraffin with a similar time interval regime. Parotid-stimulated saliva will be collected using Lashley cups, after stimulation with citric acid (2% w/v) applied with a cotton wool swab to the lateral border of the tongue at 30 s intervals. Before every appointment the patient is not allowed to eat, drink, smoke or chew gum for 90 min. Eating or drinking will interfere with the collection of unstimulated whole mouth saliva.
Also, the major salivary glands will be evaluated by ultrasound (without microbubbles). The Hočevar scoring system will be used to investigate [1] parenchymal echogenicity compared with the thyroid gland, graded 0–1; [2] homogeneity, graded 0–3; [3] presence of hypoechogenic areas, graded 0–3; [4] hyperechogenic reflections, graded 0–3 in parotid glands and 0–1 in submandibular glands; and [5] clearness of the salivary gland border,

graded 0–3, in both parotid and submandibular salivary glands. Total ultrasound score is the sum of these five domains and can range from 0 to 48. The patient will be excluded when a MALT-lymphoma is detected during this evaluation of the salivary glands.
Furthermore, the Clinical Oral Dryness Score is recorded (CODS score) is recorded.

Questionnaires regarding the mouthfeel, patient reported disease activity and pain are handed out:
- Mouthfeel: Xerostomia Index Score (XI)
- Patient reported disease activity: ESSPRI questionnaire.
- Pain-score: a Dutch version of the McGill Pain Questionnaire (MPQ).

Every volunteer is marked with a number 1-10 (based on order of application) for anonymization purposes.

T0 (Intervention appointment, application of microbubbels and ultrasound)
In every patient, under local anaesthesia, a US-guided infusion of microbubbles (SonoVue, Bracco Imaging SpA, Milan, Italy) into the parotid and submandibular glands will be performed followed by activation of the microbubbles by US.
A mixture of 0.3 ml of a second generation contrast agent (SonoVue®, Bracco, Milan, Italy) consisting of stabilized microbubbles of sulphur hexafluoride and 9.5 ml (0.9% w/v NaCl) will be used as the irrigation solution. After the orofice of the salivary gland duct to be treated is located, 0.5-1.0 ml of 4% (w/v) articaine with 1:100,000 adrenaline (Septanest; Septodont, Saint-Maru-des-Fosses, France) is injected submucosally near the papilla. Next, the endoscope is properly positioned in the salivary duct (Figure 1) under echoscopic guidance. Sialendoscopy with continuous ultrasound imaging will be performed using 0.8 or 1.1 mm diameter Erlangen sialendoscopes (Karl Storz GmbH & Co., Tuttlingen, Germany)..
Sialendoscopy is always started by flushing the salivary duct system and filling it with approximately 2 ml of irrigation solution to unfold the ducts. During sialendoscopy, irrigation fluid will continuously drain in a retrograde manner from the duct system via the ostium into the oral cavity and it is removed from the oral cavity by suction. Therefore, the irrigation fluid has to be replenished regularly throughout the procedure. For this, a small volume of irrigation fluid will be applied whenever the ducts collapse. This strategy results in an average application rate of about 0.5 ml irrigation fluid per minute. Stronger and longer-lasting bursts of irrigation may be necessary during endoscopy to flush out plaques and microsialoliths from the salivary duct system and open strictures. On the surgeon’s instruction, the assisting nurse will perform intermittent flushing by manual pressure on the 10 ml syringe. Finally, an intraductal bolus injection of the remaining irrigation solution will be administered under direct vision into the salivary glands and maintained in the glands by temporarily (± 10 min) occluding the ductal orifices with a microvascular clamp. During the procedure, continuous ultrasound imaging will be performed using a local transdermal US device to visualize the glands, including the location of strictures and occlusions. This will be performed at a fixed US resonance frequency of 9 MHz, performed under low US mechanical index settings (e.g., MI: 0.1), to avoid disruption and premature activation of the bubbles. It will be visualized how far and how quick the microbubbles enter the ductal system of the salivary glands and the effect of the sialendoscopic rinsing procedure on strictures (i.e., occlusions or blockades) will be monitored.

T1 (1 week after intervention)
- AEs and SAEs are recorded continuously.
- Collection and storage of UWS, SWS, and SPF.
- CODS score is recorded.
- The patient fills out questionnaires regarding xerostomia and SS symptoms score: XI score, ESSPRI score.
- Pain-score: McGill Pain Questionnaire (MPQ).
- Changes in medication use are noted.
- Sonographic (ultrasound; without microbubbles) evaluation of salivary gland alterations (Hočevar score).

T2 (2 weeks after intervention)
- AEs and SAEs are recorded continuously.
- Collection and storage of UWS, SWS, and SPF.
- CODS score is recorded.
- The patient fills out questionnaires regarding xerostomia and SS symptoms score: XI score, ESSPRI score.
- Pain-score: McGill Pain Questionnaire (MPQ)
- Changes in medication use are noted.

T8 (8 weeks after intervention)
- AEs and SAEs are recorded continuously.
- Collection and storage of UWS, SWS, and SPF.
- CODS score is recorded.
- The patient fills out questionnaires regarding xerostomia and SS symptoms score: XI score, ESSPRI score.
- Pain-score: McGill Pain Questionnaire (MPQ).
- Changes in medication use are noted.

T16 (16 weeks after intervention)
- AEs and SAEs are recorded continuously
- Collection and storage of UWS, SWS, and SPF.
- CODS score is recorded.
- The patient fills out questionnaires regarding xerostomia and SS symptoms score: XI score, ESSPRI score.
- Pain-score: McGill Pain Questionnaire (MPQ).
- Changes in medication use are noted.
- Sonographic (ultrasound; without contrast agent) evaluation of salivary gland alterations (Hočevar score).

Intervention

CEUSS is a classic endoscopic technique combined with US imaging, specially designed for application in large salivary glands. In every patient, under local anaesthesia, a US-guided infusion of microbubbles (SonoVue, Bracco Imaging SpA, Milan, Italy) into the parotid and submandibular glands will be performed followed by activation of the microbubbles by US. A mixture of 0.3 ml of a second generation contrast agent (SonoVue®, Bracco, Milan, Italy)

consisting of stabilized microbubbles of sulphur hexafluoride and 9.5 ml (0.9% w/v NaCl) will be used as the irrigation solution. After the orofice of the salivary gland duct to be treated is located, 0.5-1.0 ml of 4% (w/v) articaine with 1:100,000 adrenaline (Septanest; Septodont, Saint-Maru-des-Fosses, France) is injected submucosally near the papilla. Next, the endoscope is properly positioned in the salivary duct (Figure 1) under echoscopic guidance. Sialendoscopy with continuous ultrasound imaging will be performed using 0.8 or 1.1 mm diameter Erlangen sialendoscopes (Karl Storz GmbH & Co., Tuttlingen, Germany).. Sialendoscopy is always started by flushing the salivary duct system and filling it with approximately 2 ml of irrigation solution to unfold the ducts. During sialendoscopy, irrigation fluid will continuously drain in a retrograde manner from the duct system via the ostium into the oral cavity and it is removed from the oral cavity by suction. Therefore, the irrigation fluid has to be replenished regularly throughout the procedure. For this, a small volume of irrigation fluid will be applied whenever the ducts collapse. This strategy results in an average application rate of about 0.5 ml irrigation fluid per minute. Stronger and longer-lasting bursts of irrigation may be necessary during endoscopy to flush out plaques and microsialoliths from the salivary duct system and open strictures. On the surgeon’s instruction, the assisting nurse will perform intermittent flushing by manual pressure on the 10 ml syringe. Finally, an intraductal bolus injection of the remaining irrigation solution will be administered under direct vision into the salivary glands and maintained in the glands by temporarily (± 10 min) occluding the ductal orifices with a microvascular clamp. During the procedure, continuous ultrasound imaging will be performed using a local transdermal US device to visualize the glands, including the location of strictures and occlusions. This will be performed at a fixed US resonance frequency of 9 MHz, performed under low US mechanical index settings (e.g., MI: 0.1), to avoid disruption and premature activation of the bubbles. It will be visualized how far and how quick the microbubbles enter the ductal system of the salivary glands and the effect of the sialendoscopic rinsing procedure on strictures (i.e., occlusions or blockades) will be monitored.

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Eligibility criteria

Inclusion criteria

- A diagnosed (by the 2016 ACR-EULAR criteria) primary or secondary Sjögren’s syndrome
- Age: ≥18 years and ≤ 75 years
- A remaining salivary flow: UWS≥0.02, SWS≥0.10 ml/min

Exclusion criteria

- A remaining salivary flow: UWS<0.02, SWS<0.10 ml/min
- When it is not possible to identify and enter the orifice of the salivary duct(s) (determined during T-6)
- Acute sialadenitis, severe illness or physical conditions interfering with the intervention
- Use of sialogogue medication (i.e. Pilocarpine)
- A history of head and neck radiotherapy
- Cardiac patients with an (suspected) acute coronary syndrome, recent percutaneous coronary intervention, acute or chronic severe [New York Heart Association (NYHA) class III/IV] heart failure, right-to-left shunts, severe pulmonary hypertension (pulmonary artery pressure >90 mmHg) or uncontrolled hypertension, adult respiratory distress syndrome or severe cardiac dysrhythmias.
- Use of Dobutamine. Sonovue should not be used in combination with dobutamine (used for heart failure) in patients with conditions that suggest cardiovascular instability where dobutamine is contraindicated.
- Presence of MALT-lymphoma in the major salivary glands

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-07-2020
Enrollment:	10
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Yes

Plan description
All collected and deidentified data will be deposited in the Dryad Digital Repository.

Ethics review

Positive opinion

Date:	16-05-2019
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 49417
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL7731
CCMO	NL68283.029.20
OMON	NL-OMON49417

Study results