Intra-operative visualization and treatment of salivary glands affected by sjögren*s syndrome using contrast enhanced ultrasound sialendoscopy (ceuss): a pilot study

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our aim is to investigate practical applicability and safety of contrast enhanced ultrasound sialendoscopy (CEUSS) in salivary Parotid and Submandibular glands affected by Sjögren*s Syndrome

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON49417

Source
ToetsingOnline

Brief title
Sialendoscopy and ultrasound

Condition

- Autoimmune disorders
- Endocrine gland therapeutic procedures

Synonym
Hyposalivation, Sjogren's Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Microbubbles, Sialendoscopy, Sjögren's Syndrome, Ultrasound

Outcome measures

Primary outcome

Main endpoints will be technical feasibility and safety of the experimental treatment. Technical feasibility will be defined as accomplishment of the experimental protocol during the procedure.

Secondary outcome

- Determination of changes, compared to baseline, of the unstimulated whole mouth (UWS) salivary flow, the stimulated whole mouth (SWS) salivary flow, and the stimulated parotid salivary flow (SPF) after performing contrast enhanced ultrasound sialendoscopy.

- Analysis of the salivary cytokine profiles (IL-1*, IL-6, BAFF, IL-12, IL-18, TNF*). Collected saliva will be analyzed because no information is available about the effect of sialendoscopic irrigation of the glands on saliva composition. The main goal of saliva collection is to monitor changes in salivary flow after the intervention. But this saliva could also be used for an analysis of changes in saliva composition related to the intervention. Hereby, waste of collected human material is prevented.

- Measurement of changes in the Clinical Oral Dryness Score (CODS), after performing contrast enhanced ultrasound sialendoscopy, compared to baseline.

- Determination of changes taking place in the reported pain, mouthfeel and clinical SS symptoms using a set of validated questionnaires (MPQ, XI, ESSPRI) (see appendices), after performing contrast enhanced ultrasound sialendoscopy compared to baseline.

- Sonographic (ultrasound) evaluation of salivary gland alterations (Ho*evar score). The echostructure of the treated glands will be graded at T-4, T1 and T16.

- EULAR Sjogren*s Syndrome Disease Activity Index (ESSDAI) score is determined at T-4, T2 and T16.

Study description

Background summary

Sjögren*s syndrome (SS) is an autoimmune inflammatory disorder of the exocrine glands highly associated with rheumatoid arthritis. The prevalence of SS is estimated at 0.15-1% of the worldwide population with a female preference (female:male ratio 9:1). SS is therefore the second most common autoimmune disease.
SS particularly affects the lacrimal and salivary glands. Severe dry mouth and eyes are frequently reported as presenting symptoms. In SS, the quantity and quality of saliva reduces progressively. Next to a reduced saliva production of the glands, also the saliva-transporting ducts are often occluded. Due to hyposalivation the patients suffer from progressive dental decay, dental erosion, severe dry mouth complaints (i.e. eating and swallowing problems, lack of taste), inflammation of the oral mucosa and lack of retention of removable

dentures. Overall, this may lead to a marked reduction in the quality of life.

In recent years, we established a promising approach to use endoscopic irrigation of the glands (sialendoscopy). In this technique the ducts of the salivary glands are rinsed with saline and cortisone and strictures (i.e. occlusions or blockades) are dilated. We showed alleviation of the oral symptoms of patients suffering from SS and restoration of salivary flow to adequate levels. However, limitations of this technique include: only a few ducts can be visualized per treatment, no diagnostic imaging (occlusions, flow) available at time of treatment and effect assessment only in follow-up.

To tackle these issues and improve our therapy, we will employ contrast-enhanced ultrasound (US) using commercially available sulphur hexafluoride microbubbles (SonoVue; Bracco SpA, Milan, Italy) combined with classic sialendoscopy. These microbubbles, consisting of 5-10 µm gas-filled particles, are used as contrast agents to demonstrate (occlusions of) fluid flow in several organs.

In our approach, the microbubbles will actually serve multiple purposes:
* We expect that the µm-size of the microbubbles facilitates penetration of virtually all ducts, thereby allowing non-invasive high-resolution US imaging of the glands, and in particular duct occlusions (where microbubbles will accumulate). Based on previous research, we expect that stasis of the contrast agent can be seen in front of the stenosis, indicating the occurrence of a stricture. The passing of the contrast agent will result in elongation of the stricture.
* The effect of the classic sialendoscopic treatment can be imaged directly by re-infusion of microbubbles, and assessing the *new* distribution pattern.
Even though the treatment we exert in the current study is technically spoken a symptomatic solution, we have provided evidence that sialendoscopy is able to restore saliva flow significantly, reducing the burden of the SS patient. Sialendoscopy is a minimal invasive technique, which is clinically accepted in the Netherlands to treat obstructive salivary gland diseases. Sialendoscopy is performed under local anaesthesia. The current project has the added value over classic sialendoscopy that it encompasses non- invasive intra-operative visualization and diagnostic imaging with no radiation exposure of the patient, and we hypothesize that the irrigation-induced local hydrostatic pressure may dissolve ductal occlusions and enhance saliva flow.

Microbubbles are widely used for various applications, both as contrast agent and as treatment modality. The use of microbubbles is also described for salivary glands but not for US-assisted contrast imaging in salivary glands affected by Sjögren*s syndrome. Therefore, and because it concerns an intervention with a registered medicine with a different indication, it is imperative that this new application is first tested for its feasibility and safety in this category of patients.

Study objective

our aim is to investigate practical applicability and safety of contrast enhanced ultrasound sialendoscopy (CEUSS) in salivary Parotid and Submandibular glands affected by Sjögren*s Syndrome

Study design

This is a single center, single-arm trial. The study will be conducted with patients diagnosed with Sjögren*s syndrome (SS) and will encompass a recruitment period of 8 months and a patient follow-up time of 16 weeks (excluding medical ethical approval, data analysis etc).

Intervention

Contrast enhanced ultrasound sialendoscopy: A mixture of 0.3 ml of a second generation contrast agent (SonoVue®, Bracco, Milan, Italy), consisting of stabilized microbubbles of sulfur hexafluoride and 9.5 ml (0.9% NaCl) will be prepared (irrigation solution).

At the start of the treatment, local anaesthesia is introduced, upon which 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. Sialendoscopy is always started by flushing the salivary duct system and filling it with approximately 2 ml 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 will be applied whenever the ducts collapse. This strategy results in an average application rate of about 0.5 ml irrigation fluid per minute (23). 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 stricture. 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 intraductally 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 ultrasound 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 (MI: 0.1) to avoid disruption and premature activation of the bubbles (see reference #13 in the protocol). It will be monitored 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. The application of the microbubbles concerns an intervention with a registered medicine with a different indication.

Study burden and risks

The burden for participating volunteers is two consultation visits followed by a visit on which the intervention is performed under local anaesthesia and several follow up visits. At every visit (except the intervention visit) the patient has to donate saliva, and the patient has to fill out questionnaires.
At T-4, T1 and T16 the major salivary glands are evaluated by ultrasound using the Ho*evar scoring system.
A reported side effect of sialendoscopy is post-operative swelling. Postoperative swelling usually occurs during the initial 48 hours and may last for 3-5 days after the procedure. A possible but rare complication is perforation of the salivary duct and the creation of a passage due to the application of excessive force.
Ultrasound is a safe and non-invasive imaging technique. The use of contrast enhanced ultrasound in salivary glands is described before in non-SS patients, either by intraductal or by venous application (12*14). Zengel et al described that the intraductal application of Sonovue microbubbles was easily to perform and no patient inconvenience, pain or side effects were detectable. About the safety and side effects of the systematic use of microbubbles there is a large body of literature available, mainly from the field of cardiology. According the EMA (European Medicines Agency) guideline, the most common side effects when SonoVue is injected into a vein (seen in up to 1 in 100 patients) are headache, nausea (feeling sick) and reactions at the injection site. In literature, a low incidence of adverse reactions to the use of Sonovue microbubbles as an ultrasound contrast agent for clinical applications in abdominal and superficial organs is found. It should be emphasized that in our study the microbubbles will not be injected intravenously but into the ducts of the salivary glands. Therefore, the microbubbles will not enter the bloodstream and we presume that the occurrence of adverse reactions, as described below, is even more limited compared to intravenous infection.
The benefit for the participating patient is a possible reduction of dry-mouth complaints and (partial) restoration of salivary flow. The application of the microbubbles concerns an intervention with a registered medicine with a different indication.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- A diagnosed (by the 2002 ACR-EULAR criteria) primary or secondary Sjögren*s Syndrome
- Age: *18 years and * 80 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

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-07-2020
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	08-05-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 26628
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL68283.029.20
OMON	NL-OMON26628