Title: NeutraSal in the Management of Xerostomia in Obstructive Sleep Apnea Syndrome patients utilizing CPAP therapy

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Abstract

Obstructive Sleep Apnea Syndrome (OSAS) is a very common disorder with a high prevalence in the general population. Common manifestations of OSAS include snoring, excessive daytime sleepiness, fatigue as well as long term sequalae like memory loss and attention deficits[1], hypertension, arrhythmias, coronary artery disease[2], congestive heart failure, stroke[3] and insulin resistance[4]. Given the significant impact of OSAS on overall health and quality of life, it is very important to treat it optimally. The treatment of OSAS most commonly involves the use of Continuous Positive Airway Pressure (CPAP) to maintain patency of the upper airway. Nonadherence rates to CPAP are variable and range from 29% to 83%[5-7] in various studies. One of the common reasons for non-compliance with CPAP usage is mouth dryness[8]. Mouth dryness or xerostomia also impairs sleep quality and overall quality of life[9] and can be further exacerbated in patients who are mouth-breathers or have underlying conditions predisposing to xerostomia. Anecdotally, in our clinical experience, approximately 80%-90% patients with OSAS on CPAP therapy complain of dry mouth. In about 1/3rd of these patients, the sensation of mouth dryness is significant and bothersome enough to decrease compliance with CPAP. The addition of heated humidification may improve the mouth dryness but has a variable impact on CPAP compliance with some recent studies showing no improvement in CPAP compliance at all[9]. Given the significant adverse effects of OSAS on health, alternative measures to improve CPAP compliance in patients with OSAS need to be considered and evaluated. . As part of this initiative, our study aims to show improvement in patient CPAP compliance with the use of NeutraSal, a supersaturated calcium phosphate rinse, targeted at treating the dry mouth associated with CPAP therapy.

Study Trial (Post-market)

NeutraSal in the Management of Xerostomia in Obstructive Sleep Apnea Syndrome patients utilizing CPAP therapy

Study Population:
Patients are male or female, ages 18-84, with a diagnosis of obstructive sleep apnea syndrome (OSAS), who have been started on CPAP treatment and have subsequently complained of dry mouth or developed worsening of a pre-existing dry mouth condition, as an effect of CPAP treatment.

Study Design:
Randomized, double- blinded, study of OSAS patients undergoing CPAP therapy designed to observe the impact of NeutraSal on compliance to CPAP therapy as compared to placebo.

Sample Size
~32 patients per site (16 in study group and 16 in placebo group)
Population
The population will be composed of patients with a confirmed diagnosis of OSAS who are on CPAP therapy, have developed new onset of dry mouth or have worsening of pre-existing dry mouth condition, as an effect of CPAP treatment, meet the other inclusion criteria and do not have any exclusion criteria.

Trial Duration
Ongoing recruitment; subjects will be followed for 12 weeks from the time of enrollment in the study.

Trial Agent and Intervention Description (If applicable)
NeutraSal, dosed 2 times per day at waking and bedtime (indications 2-10 times per day or PRN), swish and spit, daily for a term of 12 weeks.

Primary Objective
To observe the impact of NeutraSal on OSAS patients compliance to CPAP therapy compared to placebo.

Secondary Objective
To assess whether the daily use of NeutraSal will prevent or reduce dry mouth perception in patients undergoing CPAP therapy

Tertiary Objective
To assess whether NeutraSal will balance the pH of the oral mucosa long term (3 months)

Efficacy Measurements*:*

1. Compliance with use of cpap
2. Xerostomia Questionnaire
3. Resting Saliva pH Testing
4. Product Utilization based on Patient Diary

Exit Evaluation:

1. 1. Brief Physical Exam for Overall Health
2. Final collection of patient information during visit on data form
3. Final review of efficacy measurements

Study Population:

Inclusion /Exclusion Criteria

The inclusion criteria will be as follows:

1. Patient should be above 18 years of age.
2. Patients who have been initiated on CPAP therapy after an initial diagnosis of OSAS and have developed dry mouth or have worsening of pre-existing dry mouth condition, as an effect of CPAP therapy.
3. Ability to attend visits at the research site
4. Patient should be able to read and/or understand and sign the consent form be willing to participate in the research study

The exclusion criteria are as follows:

1. Patients with open mouth sores at study entry.
2. Any pathology that, based on the judgement of the researcher, could negatively affect the oral mucosa and subsequent treatment for xerostomia (immune disorders, etc.)
3. Patients using any other prophylactic mouthwashes.
4. Patients who are pregnant and/or nursing.
5. Patients becoming pregnant during the treatment period will be removed from data.
6. Patients on a low sodium diet
7. Patients currently on medication or treatment for xerostomia
8. Patients < 18 years of age
9. Hypersensitivity to any of the following ingredients- sodium chloride, sodium phosphate, calcium chloride and sodium bicarbonate

Trial drug /Interventions:

NeutraSal is a powder that when dissolved in water creates a supersaturated calcium phosphate rinse.

Placebo is a powder consisting of sodium chloride only. Sodium chloride has been chosen as a placebo because it looks like Neutrasal and can be packaged (in foil) like Neutrasal for a double blind effect.

For the study, NeutraSal or placebo will be dispensed by the investigator for the treatment length in a randomized, double-blind procedure. Patients will be provided pre-measured cups, timer to measure length of time patient gargles and patient instructions. Patients will mix product(s) at home in a clean glass or supplied pre-measured cup.

Trial Schedule:

Projected Start Date: July 1st, 2013

Patients with OSAS seen in MUSC (Medical University of South Carolina) sleep clinic who are on CPAP, meet the inclusion criteria and do not have any exclusion criteria, will be invited to participate. After obtaining informed consent, patients will be randomized to the study or placebo groups. The study sponsor, Invado pharmaceuticals will provide a randomization schedule and key. The packets of product and placebo will be numbered 1-32 based on the randomization. Patient 1 will get bag 1, patient 2 will get bag 2 and so on. The study product NeutraSal and placebo will be packed in identical bags. Both the investigators and patients will be blinded to the contents of the bags, hence this will be a double-blind study. Patients will begin taking NeutraSal or placebo at the start of therapy and continue through 12 weeks of treatment.

Patients will receive a baseline visual examination of the oral mucosa in addition to a brief physical exam by the investigators and study coordinator at visit one and receive samples of the product. Patients will be given a diary or questionnaire to record compliance to the product and Xerostomia symptom relief. Patients will be monitored by the principal investigator and the study coordinator via office visit on the baseline visit, visit at 6 weeks and a final visit at 12 weeks.

During these visits the principal investigator and study coordinator will measure the following:

- Xerostomia Questionnaire
- CPAP Compliance measured by objective CPAP downloads as outlined in the follow up visits section
- Product Utilization and Compliance to Dosing (Patient Diary Reviewed)
- Adverse Effects
- Resting salivary pH

Schedule of Study Events:

	Baseline Visit	**6 Weeks**	**12 Weeks**
Medical History	X		
Brief Physical Exam	X	X	X
Pregnancy Test	X	X	X
Informed Consent Form	X		
Inclusion/Exclusion Criteria	X		
Treatment Administration	X	X	X
Xerostomia Questionnaire	X	X	X
Resting pH	X	X	X
Compliance Report/ Patient Diary	X	X	X
Adverse Effect Monitoring	X	X	X

Data collection instruments are included in the IRB submission.

Screening Visit/ Initial Visit

During this visit, OSAS patients on CPAP who are eligible for study enrollment will be given information about the study. An informed consent form will be reviewed and signed. Subjects will receive a brief physical medical exam and a baseline visual examination of the oral mucosa. Once enrolled in the research study, patients will receive either medication or placebo in a randomized selection. Patients will also complete an oral questionnaire on the state of xerostomia. Researchers will do a baseline pH test of the oral mucosa. Patients will be

instructed on proper use of neutrasal or placebo. Patients will be given a diary or questionnaire to record compliance to the product and Xerostomia symptom relief.

Follow Up Visits

Patients will complete an oral questionnaire on the state of xerostomia since the initial visit and compliance with CPAP therapy will be reviewed by history and by objective CPAP compliance downloads. Researchers will also review the patient diary for compliance to dosing for medication. CPAP compliance will be recorded as the number of days that the patient used CPAP for ≥ 4 hours/day and the average number of hours of nightly usage. CPAP compliance downloads are provided by durable medical company (DME) providers and usually indicate both of these measures. The dates between which the compliance is measured are also indicated on the compliance downloads provided by the DME providers. CPAP compliance will be recorded on the 2nd visit at 6 weeks and the 3rd visit at 12 weeks. Every effort will be made to obtain CPAP compliance from the date that subjects are started on neutrasal/placebo until the dates of the study visits. If CPAP compliance for the entire period of 6 weeks before the 2nd visit and 3 months before the 3rd visit is not available, then any compliance data from a point after subjects received the study drug till a date in the 5-7 week period around visit 2 and in the 10-12 week period around visit 3 will be recorded. The date range of the available compliance data will also be recorded.

If any patients miss follow-up visits, then phone follow-up will be done to obtain information about their product utilization, compliance to dosing and xerostomia symptom relief. CPAP compliance downloads for these patients will be obtained from the DME providers.

Adverse Event Reporting:

Adverse Event (AEs) and Serious Adverse Event (SAEs) will be reported immediately, if suspected to be related to treatment.

Subject Withdrawals:

Subjects will be advised that they are free to withdraw from the study at any time for any reason, or, if necessary, the Investigators may withdraw a subject from the study, according to the following criteria, to protect the subject's health:

- Intolerable adverse effects
- Major violation of study protocol procedures
- Non-compliance with protocol
- Subject unwilling to proceed or consent is withdrawn
- Pregnancy

Statistical Analysis Plan:

This is a double-blind, randomized, intention to treat, controlled clinical trial comparing Neutrasal to Sodium Chloride placebo in a 1:1 randomization. The primary analysis is a comparison of CPAP compliance measured by days CPAP was used for ≥ 4 hours per night over 12 weeks.

The secondary analyses include:

1)CPAP compliance as measured by average number of hours of daily CPAP use.

2) improvement in the total score of the Xerostomia questionnaire measured at baseline and 12 weeks.
3) Change in resting salivary pH between baseline and 12 weeks.

Statistical analysis will be performed using two sided t-test with $p<0.1$ being considered significant for this pilot study. Missing data will be treated by use of last data carried forward methodology.

Sample size determination
This is a pilot study in which there are no previous data to determine an accurate sample size that would definitively prove or exclude the possibility of a treatment effect. We estimate the treatment to be effective at improving CPAP compliance in 25% of subjects. This would translate to the same estimated increase in number of days in which CPAP is used for $\geq$ 4 hours. Therefore, a sample size of 30 subjects is needed to obtain an 80% confidence level with a response rate of 25%. We estimate that 2 subjects will drop out, therefore we will need 32 subjects for this study.

Informed Consent Process:
The language and writing of an informed consent will be at a 6th grade level.
No potentially vulnerable subjects will be enrolled in the study, such as, pregnant and lactating women, children, prisoners, cognitively impaired and critically ill subjects.

Privacy and confidentiality:
Human subjects' names will be kept on a password protected database, and will be linked only with a study identification number for this research. There will be no patient identifiers. All data will be entered into a computer and kept on password protected network storage. Hard copies of the records collected as a part of this study will be kept in a locked office. Only the study personnel will have access to the study records.

Risk/Benefit:

Risk to participants: It is expected that there will be no risk or a limited risk to patients due to the safety profile of NeutraSal (i.e., NeutraSal can be swallowed with no adverse effects expected) and the placebo (sodium chloride). There has been only one adverse effect reported to the FDA due to NeutraSal till today which is the development of mouth sores in one patient after 20 days of use. It is not known whether NeutraSal directly caused the mouth sores as the patient was on other medications concomitantly. Some subjects have reported a "too salty" taste of NeutraSal. The experience of our local rheumatologists at MUSC is that most Sjogren's syndrome patients have liked NeutraSal although a few have reported some "burning" sensation in the mouth. Patients on a low sodium diet will be excluded. There are no interactions between NeutraSal and other medications or products. Patients with a hypersensitivity to any of the following ingredients- sodium chloride, sodium phosphate, calcium chloride and sodium bicarbonate will be excluded from this study.
If an allergic reaction or adverse effect does occur, the subjects will be asked to stop taking the medication immediately, to seek medical help and to inform the study personnel.

Benefits to Participants
This study presents the prospect of a direct benefit to the participants in the reduction of xerostomia which will allow better compliance with CPAP treatment for OSAS. Patients will receive compensation of a $20.00 (gift card) after completion of each study visit.

Data Safety Monitoring:
NeutraSal is an approved product with few known adverse effects; thus, this study is considered minimal risk. Diligent safety monitoring will be conducted by the PI throughout the conduct of this study in compliance with the required IRB continuing review process including tracking of subject accrual, timely reporting of deficiencies related to informed consents or protocol deviations, conflicts of interest or changes in personnel. Any action resulting in a temporary or permanent suspension or delay of the study will be reported to the IRB. The PI is responsible for reporting any reasons outside the planned study design such as noncompliance with the protocol or if there is any delay in the initiation of the study due to administrative reasons.

Drug Storage Conditions:
NeutraSal is a powder in individual packets. Placebo is a powder in individual packets. NeutraSal and placebo are to be stored in a location with normal room temperature and avoidance of moisture.

Conflict of Interest:
There is no expected conflict of interest.

Publication and Presentation Plans:
Abstract presented as a poster or an oral presentation at upcoming national/international Pulmonary, Critical Care and Sleep meetings, dental meetings and possible publication.

STUDY SIGNIFICANCE:
Xerostomia is excessive dryness of the mouth. It is due to insufficient saliva secretion.

Xerostomia is often accompanied by buccal symptoms and signs such as impaired sense of taste, fetid breath and mouth ulcers, and it disturbs functions such as speech, chewing and swallowing. Because of reduced salivary secretion, there is disturbance of the microbial colonization of the buccal cavity, increased demineralization and decreased remineralization of the teeth, impaired retention of dentures, dehydration of the mucosa and reduced lubrication of the buccal mucosa. These complications may take the form of dental caries, candidiasis, atrophy and feelings of burning of the mucosa, difficulty retaining dentures, impaired speech and swallowing and impression of decreased or impaired sense of taste. Xerostomia has significant harmful effects on the buccal cavity and on the quality of life of patients. Xerostomia is one of the major factors affecting compliance with cpap therapy.

Treatments of xerostomia are saliva substitutes and saliva stimulants. NeutraSal is a saliva substitute. Obstructive Sleep Apnea Syndrome (OSAS) is a common disorder with a prevalence of (defined in this study as an apnea-hypopnea index (AHI) of 5 or higher and excessive daytime sleepiness) to be 2% in women and 4% in men in the 30-60 year age group[10]. The estimated prevalence of an AHI of 5 or greater with no symptoms was even higher at 9% in women and 24% in men in the same age group. Thus OSAS is a major public health problem.

Common manifestations of OSAS include snoring, excessive daytime sleepiness and fatigue. In addition, emerging data has linked OSAS to neurocognitive deficits such as memory loss and attention deficits[1], hypertension, arrhythmias, coronary artery disease[2], congestive heart failure, stroke[3] and insulin resistance[4]. Given the significant impact of OSAS on overall health and quality of life, it is very important to treat it optimally.

The treatment of OSAS most commonly involves the use of Continuous Positive Airway Pressure (CPAP) to maintain patency of the upper airway. CPAP being noninvasive and very effective at treating OSAS, is generally considered first line treatment for OSAS, in the absence of any contraindications to its use. CPAP machines blow mildly pressurized air into a connected tube and a mask or other attaching device that extends from the other end of the tube. This pressurized air gently opens the airways and keeps them open. Patient compliance with CPAP usage is often limited by mouth dryness which is a common side effect. This may be further exacerbated in patients who are mouth-breathers or have underlying conditions predisposing to Xerostomia. Heated humidification may have some effect on improving the mouth dryness but does not eliminate it entirely in most cases, thus decreasing patient adherence to CPAP therapy. Neutrasal is a supersaturated calcium phosphate rinse which has been shown to improve xerostomia in Sjogren's syndrome patients. Our study will attempt to show improvement in patient CPAP compliance, salivary parameters such as pH and salivary flow and overall quality of life with the use of NeutraSal, which will be used to prevent/treat the xerostomia associated with CPAP therapy.

References:

1 Verstraeten E. Neurocognitive effects of obstructive sleep apnea syndrome. Curr Neurol Neurosci Rep 2007; 7:161-166

2 Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005; 365:1046-1053

3 Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001; 163:19-25

4 Meslier N, Gagnadoux F, Giraud P, et al. Impaired glucose-insulin metabolism in males with obstructive sleep apnoea syndrome. Eur Respir J 2003; 22:156-160

5 Weaver TE, Kribbs NB, Pack AI, et al. Night-to-night variability in CPAP use over the first three months of treatment. Sleep 1997; 20:278-283

6 Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 2008; 5:173-178

7 Sarrell EM, Chomsky O, Shechter D. [Treatment compliance with continuous positive airway pressure device among adults with obstructive sleep apnea (OSA): how many adhere to treatment?]. Harefuah 2013; 152:140-144, 184, 183

8 Bachour A, Maasilta P. Mouth breathing compromises adherence to nasal continuous positive airway pressure therapy. Chest 2004; 126:1248-1254

9 Ruhle KH, Franke KJ, Domanski U, et al. Quality of life, compliance, sleep and nasopharyngeal side effects during CPAP therapy with and without controlled heated humidification. Sleep Breath 2011; 15:479-485

10 Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328:1230-1235