NCTXXXXXXXX

Adherence in Global Airways - Difference Between Structured and Systematic Nursing Supervison vs Usual Care.

Abbreviations

ACT - Asthma Control Test

ACQ-7 Asthma Control Questionnaire

Adherence - Patients adherence to their non pharmacological/pharmacological treatment

CRS -Chronic Rhinosi Chronic sinusitis

CRSsNP - Chronic sinusitis with no nasal polyps

CRSwNP Chronic sinusitis with nasal polyps

ESS - EPWORTH SLEEPINESS SCALE

Global Airways - Lower and upper respiratory diseases (asthma, rhinitis and CRS/CRSwNP/CRSsNP)

HADS - Hospital Anxiety and Depression Scale

MARS-5 - Medication adherence report scale

MARS-5-L - Medication adherence report scale - lung

MARS-5-N - Medication adherence report scale - nose

miniAQLQ - Mini asthma quality of life questionnaire

miniRQLQ - Mini Rhino conjunctivitis Quality of Life Questionnaire

RCT - Randomised Controlled Trial

SNOT-22 - The Sino-Nasal Outcome Test 22

STARR-15 - Standard test for asthma, rhinitis and chronic rhinosinusitis (15 questions)

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Introduction

There is a strong case for treating diseases of both the upper and lower airways (global airways) simultaneously, because they share the same inflammatory mechanisms (1,2). About 9% have chronic sinusitis (CRS) and 4% of the Danish population are diagnosed with (CRS) with nasal polyps (CRSwNP) and 7-10% have asthma. CRS has a multifactorial background, with CRSwNP characterized by Type 2 inflammation, and approximately 50% with Type 2 CRSwNP also have co-morbid asthma (3). Well-treated CRS has an impact on asthma control, and well-treated asthma has an impact on CRS.

The above can be strongly supported by daily clinical practice, where these patients experience high levels of morbidity, which often significantly affect their daily lives and thereby also result in a markedly reduced quality of life. Several studies show that patients with asthma have low adherence (4,5), but only a few if any of studies are available on adherence in CRS. Patients rely on seeing different specialists (otolaryngologist and pulmonologist) to optimize their adherence in the upper or lower airways. This provides an opportunity

to investigate patients' adherence with diseases of the global airways, and analyse whether patients' adherence with diseases of the global airways can be improved and whether this will contribute to increased disease control and significantly improved quality of life.

Purpose
To investigate the effect of systematic and structured nursing guidance in patients with global airways disease, CRSwNP and asthma primarily on adherence (measured on MARS-5- L/N), where the maximum score is 50 at 100% adherence for both diseases. As well as whether there is a change at the minimum in adherence in patients who receive systematic and structured guidance on disease and treatment compared to usual care which does not include structured guidance.

Hypothesis and research questions
Patients with respiratory diseases can improve their adherence to their non-medical and the medical treatment for CRSwNP/CRS and asthma by systematic and structured nursing guidance compared to patients who did not receive the above guidance.

In a randomized study, we will investigate whether the level of adherence measured by the questionnaire MARS-5-N and MARS-5- L in patients with CRSwNP/CRS and asthma can be improved by 5 points after systematic and structured nursing guidance at baseline visit and controlled after four months - compared with those patients who have not received the above guidance.

Outcomes
The primary outcome is to investigate whether the adherence rate measured by the MARS-5-N/L questionnaire in patients with CRSwNP and asthma can be improved by 4 points after systematic and structured nursing guidance at the initial visit and controlled after four months - compared with those patients who have not received the above guidance.

Secondary outcomes
- To demonstrate whether improved adherence can improve their sleep measured on a Epworth Sleepiness Scale - messured during a 4 month follow-up visits.

- To demonstrate whether improved adherence can improve their SNOT22 score by 9 points or more messured at a 4 month follow-up visits.

- To demonstrate whether improved adherence can improve their asthma control as measured by the ACQ messured at a 4 month follow-up visits.

- To demonstrate whether improved adherence can improve their asthma control as measured by ACT - measured at a 4 months follow-up visit.

- To demonstrate whether improved adherence can improve their quality of life as measured by the mini AQLQ messured at a 4 months follow-up visit.

- To demonstrate whether improved adherence can improve their anxiety/depression as measured by HADS - messured at a 4 months follow-up visit.

- To demonstrate whether satisfactory adherence (i.e. 80%) can improve their nasal symptoms measured via SNOT22 and STARR-15 - messaured at 4 a months follow-up.

- To demonstrate whether satisfactory adherence (i.e. 80%) on lung measured via MARS-5-L and poor adherence on nose measured via MARS-5-N improve their respiratory symptoms measured ACQ or ACT - messsured at a 4 months follow-up.

- Demonstrate differences in patients with three conditions (asthma, CRS and allergic rhinitis) measured via STARR-15 meassured at a 4 months follow-up visit.

Background

CRS is a condition of chronic inflammation of the nose and sinuses. CRS can appear in the nasal polyps (CRSwNP) and without polyps (CRSsNP)(2,3). 9% of the Danish population is affected by CRS, and approximately 4% are estimated to be diagnosed with CRSwNP (4). The diagnosis is based on the patient's symptoms and objective signs of inflammation in the nose and sinuses. Symptoms include nasal congestion or nasal secretion that runs forward or backward, decreased air passage, decreased sense of smell, pain/pressure around the nose, forehead or eyes. For the diagnosis to take place, the above symptoms must have been present for more than 12 weeks. To diagnose CRS, there must be secretions or reduced air passage through the nose (6,7). Approximately 40% of CRS patients in primary care have asthma, whereas 65% referred to hospital have asthma (8).

CRSwNP that is not satisfactorily controlled has a significant impact on quality of life (9,10). It is often characterized by type 2 inflammation, i.e. increased numbers of eosinophils in the mucosa of the sinuses and nasal polyps - as well as comorbidities e.g. asthma, ASA/NSAID intolerance (N-ERD) and allergies (3). CRSwNP can be treated both surgically and medically. Basic medical treatment of CRS includes daily saline irrigation and application of nasal steroid. In the case of nasal polyps, systemic steroid (tbl. prednisolone/inj. betamethasone) may be added as a course, and never as a fixed treatment (3,6). Some patients receive 1, 2 or 3 courses annually for several years, which is accompanied by many systemic side effects (1,2,11). If medical treatment is not optimal, patients may be offered surgical treatment -endoscopic sinus surgery (ESS)(2,3). The goal is the removal of polyps in the nose and sinuses, to create better air passage.

Comorbidity

In patients with CRS, attention should also be paid to comorbidity due to the interplay between the upper and lower airways. Patients with uncontrolled CRSwNP often suffer from a high burden of disease (9). Asthma and CRSwNP often interact negatively. Therefore, patients should also be evaluated for asthma. Patients with CRSwNP and type-2 inflammation (high eosinophil cell count in the blood or mucosa of the nose) are

more likely to have recurrence of CRSwNP after surgery than patients with low eosinophil cell count (3). Patients with asthma may also experience more rapid recurrence of their polyps after surgery than patients who do not have asthma.

Asthma

Asthma is a chronic inflammatory respiratory disease. It is characterized by chronic airway inflammation, airway hyperactivity and variable airway obstruction (12). It is estimated that over 300 million people world-wide suffer from asthma, of wichic most are born and raised in the Western world, which has a major impact on the economy (5). Symptoms of asthma include coughing, wheezing, shortness of breath, chest tightness, etc., and can vary in intensity. The diagnosis is made on the basis of disease history and objective findings, e.g. spirometry, FeNO measurement, provocation tests, and peak flow test (12).

Adherence

The term adherence describes the patient's compliance with the treatment strategy developed in consultation with a practitioner. The patient is considered an active participant in his or her treatment. Adherence can be measured for both pharmacological and non-pharmacological treatment. The WHO classifies measures of adherence as subjective and objective (13,14). Objective measures include measures such as pill counts, electronic monitoring (common medical card) or biochemical measures (e.g. blood tests) (13). Subjective measurements include those that require assessment by, for example, the doctor, nurse or patient. Self-reporting by the patient or assessment by the healthcare professionals are the most common methods used to assess patient adherence. MARS-5 is a subjective tool that can be used to measure patient adherence - developed by Professor Rob Horne (15,16). The MARS-5 is a generic tool. It has been validated in many different clinical settings, e.g. in patients with asthma (17). The MARS-5 consists of five questions describing patient adherence to their medical treatment. Question 1) "I forget to take them", question 2) "I change the dose", question 3) "I stop taking them for a while", question 4) "I decide to skip a dose" and question 5) " I take less than instructed". Patients are asked to rate their adherence to their medication on a 5-point scale ranging from "always" to "never" (1-5 points). The total score on the scale goes from 5 (lowest compliance) to 25 points (macsi-mal compliance).

Poor adherence is particularly seen in long-term treatment among chronic patients, underlining the importance of focusing on sustained adherence in these patients (18). Some patients stop their treatment when they have symptoms under control, after which an exacerbation occurs. They resume their treatment with the feeling that "it is not helping" because they get worse (19). The WHO estimates that only 50% of patients receiving long-term pharmacological treatment for their chronic diseases are adherent to their treatment (19,20). Adherence in asthma and COPD has been shown to vary between 22%-78% (5,19). Patients with asthma receive information, guidance, and training related to their disease in the context of "usual care" in many places. Patients' adherence to pharmacological treatment depends on their age, their level of education, their knowledge of asthma, how often they have to take medication, whether the medication is easy to take,

and how their communication is with the practitioner (19,20). Adherence to inhaled medications is lower than to oral tablets or injectable medications. The more complex and the more times the patient has to remember to take the medication, the harder it is to establish optimal adherence (19,20).

CRSwNP a chronic disease like asthma, where low adherence is often seen in mild to moderate cases compared to severe cases of CRSwNP (21). However, the clinical perception is that not all patients take all their daily doses, but few scientific studies have focused on this. The difficulty in treating CRS is that the patient must apply nasal steroid 1-2 times daily as well as it must be combined with nasal saline irrigation at least once daily. Decreased adherence is led by poor disease control. It is therefore important to support and strengthen patient adherence to CRS and asthma in order to achieve good disease control (21).

Population and recruitment

The study population consists of patients referred to the Respiratory Clinic in the Department of Ear, Nose and Throat Surgery and Audiology, Rigshospitalet. Patients are recruited by initial visits to the Respiratory Clinic, where they receive oral and written information about the project. If patients wish to participate, they must complete a written consent form for participation in the project. In order to be included in the study, the following inclusion and exclusion criteria must be met:

Inclusion criteria	Exclusion criteria
Adherence to MARS- 5 L/N ≤35 at first visit	Adherence to MARS-5- L/N >35 points at first visit
Diagnosed with asthma (with and without allergic rhinitis) at initial visit	Do not have smartphone
Able to use smartphone	Does not read or speak English
ACQ ≥1.2 or ACT≤15 (partially uncontrolled asthma)	Other illness requiring regular medication
Be over 18 years of age	Pregnancy and pregnancy that started during the study time period
SNOT-22 score ≥35	Servere psychological comorbidities
Diagnosed with CRSwNP	

Material and method

The study is a randomized trial with a control group and an intervention group. Patients will be randomized via Research Electronic Data Capture (Redcap), a secure web application for building and managing databases and online questionnaires. The system was developed at Vanderbilt University, which released the first version in 2008 (22). Patients will be randomized to the control or intervention group. Randomization will be stratified by gender. Patients in the intervention group will receive systematic and structured nursing guidance regarding their adherence, which includes proper use of nasal irrigation once or twice daily, nasal steroid/drops, use of inhaled medications, follow-up of smoking status. The intervention group will receive guidance videos which have been prepared prior to the study and will be standard for the intervention group. Guidance videos will cover the correct use of nasal irrigation, inhalation steroid, and nasal steroid/drops. The control group and intervention group will receive twice a week text message reminders to take their medications and to rinse their nose.

Their adherence will be measured via MARS-5-N and MARS-5-L f. Total MARS-5-N/L will be measured at their initial visit and four months after teaching or usual care. The same form will be given at both visits. Patients in the control group will not receive systematic and structured nursing care regarding their adherence, but their adherence will be measured via MARS-5-N and MARS-5-L max score is 50 when measuring a adherence in global airways. In a pilot study, mean (SD) 20.4 (6.28) is found for MARS-5-L, and for MARS-5-N mean 20.7 (5.57) is found. 41 points correspond to 80% of total of both MARS-5-L and MARS- 5-N. A satisfactory adherence should be 80%. In another pilot study, patients were measured twice with at least one month in between. Here, the mean of the inter-individual difference at MARS-5-L/N first and second time is equal to 5.34(2.62). These two pilot studies will be used for the final power calculation.

Statistics data analysis and power calculation

The statistical analysis of data is performed using IBM SPSS Statistics. Results will be presented as mean, SD, range and 95% CI. The parametric data will be compared using paired and unpaired tests, and non-parametric data using Wilcoxon Signed-Ranks Test and Mann-Whitney Test, respectively. Categorical variables are tested by chi-square test. A P-value <0.025 is considered significant for a pooled MARS-5-N and MARS-5-L For a pooled MARS5-L/N questionnaire, the total score would be 25x2= a total of 50 points theoretically. A safe difference is calculated from the intraindividual difference detected in the pilot study (mean 5.34 (2.62)) , but based on the pilot study an SD and mean are calculated on the difference between MARS-5-L/N, which corresponds to an SD 5.34 and mean 2.62. With a MIREDIF of 5 and the largest SD of 6.28 by single measurement with a p-value of 0.025% (0.05/2) because there are two schedules and a power 80%, this would require 36 patients in each group including a dropout of 20%.

In addition, ensuring that MARS-5-N/L are both above 80% (the standard requirements for good adherence); and hoping for 100% adherence in the intervention group, versus 80% in the control group, this would require 39 in each group. - And including the 20% dropout rate, the total population would be 47 in each group.

Project participants
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Risks and side effects
There are no serious side effects associated with participation in the trial. There may be a risk that patients in the control group of the study may have a worse prognosis/prognosis than patients achieving good adherence (80%) in the intervention group. To reduce this risk, patients in the control group are offered the same guidance as those in the intervention group at the end of the trial.

Information from patient records
No personal data will be collected from patient records. Data included in the study are from patient questionnaires and from results of clinical objective tests.

Processing of personal data
The project is carried out in compliance with the Data Protection Regulation and the Data Protection Act.

Economy
The patients are part of clinical outpatient treatment, at the Department of Ear Nose and Throat Surgery and Audiology, Rigshospitalet, and there is no increased financial consumption in connection with this, fund funding has been sought for additional work for the nurse.

Conflicts of interest
There are no financial conflicts of interest to report related to this project.

Publication of results
It will be made public in various journals and congresses.

Scientific ethical considerations
The study will be conducted according to the Helsinki Declaration. The project has been notified to the research directory of the Capital Region, Pactius, as the Capital Region is the data controller.

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Informed consent for participation in a health science research project

Research project title: Adherence in global airways – difference between structured and systematic nursing supervison vs usual care - a randomized controlled trial

Trial participant declaration of consent:
I have received written and oral information and I know enough about the purpose, the method, the advantages, and the disadvantages of the trial to give my consent to participate in the trial.

I know that it is voluntary to participate and that I can withdraw my consent at any time without losing my present and future rights to receive treatment.

I give my consent to participate in the research project and have received a copy of the declaration of consent, as well as a copy of the written information about the project.

Name of the trial participant: _____

Date: _____ **Signature:** _____

You will be informed if significant new information regarding your health is disclosed during the research project. If you request **to not be informed** about significant new information regarding your health that is being disclosed during the research project, please tick here: _____(x)

Would you like to be informed about the results of the research project and any consequences it might have for you?
Yes _____(x) **No** _____(x)

Would you like to receive text messages from Department of Otorhinolaryngology, Head and Neck Surgery & Audiology with reminders to take your medication and fill out and complete the diary?

Yes _____(x) **No** _____(x)

Declaration from the person providing information:
I declare that the trial participant has received oral and written information about the trial.
I believe that sufficient information has been provided in order to make a decision regarding participation in this trial.

Name of the person providing information: _____

Date: _____ **Signature:** _____