Study Protocol

Official Title: Treatment of Pediatric Patients That Lost Sense of Smell Due to COVID-19

ClinicalTrials.gov ID (NCT number): NCT04964414

IRB ID: STUDY21050012

Protocol Date: 25Sep2022

Scientific Background

The novel coronavirus disease (COVID-19) has a multitude of presenting symptoms, including anosmia (loss of smell) and dysosmia (disordered smell perception). Altered smell has been observed in children as well as adults (1,2). Smell retraining using commercially available essential oils is an established method for improving olfactory function in patients with post-viral or other etiologies of anosmia/dysosmia (3). Budesonide is a steroid that is commonly used as a nasal spray for treatment of allergic rhinitis. It can also reach more distal locations in the nasal cavity and be administered at higher doses via nasal irrigation; this application has been used to decrease sinonasal inflammation, especially in patients who have undergone sinus surgery. A randomized controlled trial demonstrated that a greater proportion of patients who underwent budesonide irrigation + smell retraining had significant improvement in olfactory function compared with those who underwent saline irrigation + smell retraining (4). By decreasing (even subclinical) inflammation, budesonide may improve access to olfactory epithelium and nerves and thereby increase the efficacy of smell retraining to rebuild neural connections.

Currently, the standard of care at our institution is to recommend smell retraining and/or budesonide treatment for children and young adults presenting with prolonged olfactory dysfunction after presumed or confirmed COVID infection. However, there are no studies examining whether these treatments restore the ability smell in this cohort. Therefore, we propose to objectively measure smell using the University of Pennsylvania Smell Test (UPSIT), assess nasal symptoms using the Sino-nasal Outcome Test-22 (SNOT22), and subjectively quantify smell dysfunction on a 0-10 scale in children and young adults with at least 2 months of loss of smell following COVID infection. As the current COVID-19 pandemic threatens to become endemic, this will provide crucial information regarding the best practice for treating refractory olfactory dysfunction in this population.

1. Rusetsky et al. (2021) Laryngoscope; 131(8):E2475-E2480
2. Concheiro-Guisan et al. (2021) Int J Pediatr Otolaryngol; 140:110539
3. Patel et al. (2017) Laryngoscope Investig Otolaryngol; 2(2):53-56
4. Nguygen and Patel. (2018) Int Forum Allergy Rhinol; 8(9):977-981

Study Objectives

The purpose of the study is to determine an effective treatment for children and young adults with anosmia (loss of smell)

Hypothesis 1: There will be no difference in regaining loss of smell determined by the UPSIT smell identification test in 8 weeks between those assigned to the smell retraining versus those assigned to the smell retraining plus steroid irrigations.

Study Design & Methods

Design: Prospective randomized clinical trial

Methods:

Researchers will screen all potentially eligible patients that have 'loss of smell' as their reason for visit at UPMC Children's Hospital of Pittsburgh Division of Pediatric Otolaryngology.
At the initial consult appointment at the Division of Pediatric Otolaryngology, listed study team members will perform a smell identification test called the UPSIT (University of Pennsylvania Smell Identification Test) and give the SNOT-22 (Sino-Nasal Outcome Test-22) survey. The UPSIT is a 40-item scratch and sniff test with a four-choice multiple choice question on each of the 10 pages in the booklet. Indication of smell loss can be determined - anosmia (total loss) and mild, moderate, or severe microsomia and a detection for malingering. The SNOT-22 is a 22 question survey that asks about symptoms and social/emotional consequences of a nasal disorder. The survey is on a 6 point scale - No problem (0), very mild problem (1), mild or slight problem (2), moderate problem (3), severe problem (4), and problem as bad as it can be (5).

A randomized clinical trial will be performed with two arms for those that have lost their sense of smell for at least 8 weeks: 1) smell retraining for 8 weeks 2) smell retraining + Budesonide irrigations for 8 weeks. Smell retraining consists of choosing 4 scents each week and smelling each item for 15 seconds very close to the nose once a day. Budesonide irrigations will be done once a day by pouring 0.5mg/2ml of Budesonide into a irrigation bottle with saline and irrigating the nose. Participants may do the therapies at any point during the day.

Children and young adults ages 6 to 21 will be enrolled with 30 children block randomized in each arm, in which up to 10 children in each arm will be those who did not have a positive COVID-19 antigen test or confirmed COVID-19 by history. COVID-19 testing will be used for randomization purposes, but will not be limited to testing due to the inclusion of confirmation by history.

Two groups of subjects for study inclusion:

- Group 1: COVID-19 by clinical history or lab testing (n=40 (20 randomized to each group)). Those with COVID-19 confirmation by clinical history may not have had a COVID-19 positive test.
- Group 2: Those that did not have COVID-19 by clinical history or lab testing (n=20 (10 randomized to each group)). These subjects may have had a negative COVID-19 test or no clinical history of COVID-19.

Each child, with the help of their parents, will do the assigned therapy and fill out a daily Smell Diary. The child will pick 4 scents each week to perform the smell retraining each day that week. The child or parent will check mark every day that the 4 scents were smelled. The scents do not have to be new each week. Once a week the child will rate their loss of smell on a scale from 0 (no loss) to 10 (total loss).

Researchers will check in with the parent or participant on weeks 3, 5, and after the 8-week period. Families will return the Smell Diary at their standard of care follow-up appointment at 8 weeks (range 8 to 12 weeks). The UPSIT and the SNOT-22 will be given at the follow-up appointment. If the participants' sense of smell did not return to baseline at the follow-up, they will be asked to return at 6 months after the initial consult. If the participants' sense of smell has

still not returned at the 6-month appointment, they will be asked to follow-up at 1 year after the initial consult. The UPSIT and SNOT-22 will be given at each of these appointments. If smell was not a baseline at 8 weeks, listed investigators will call the subject or subjects' parents at 6 months and 1 year after the initial appointment to check-in and for a reminder to schedule a follow-up appointment.

If participants do not have an 8-week follow-up visit, they may be mailed an UPSIT to complete at home and return by mail. They may also complete the SNOT-22 by mail or phone, and they may return the smell diary by email.

If patients were initially randomized to the smell retraining only, after the initial 8-12 weeks of therapy they may be prescribed budesonide as part of standard of care to maximize medical management as needed. We will invite participants to fill out a new smell diary during this time and we will collect any data available from the smell diary, UPSIT, and SNOT-22 at their standard of care visit after 8-12 weeks of budesonide irrigation. Patients who have already completed more than 12 weeks of smell retraining will not be included in this arm; although budesonide may be prescribed based on physician discretion, data will not be collected following budesonide treatment.

Eligibility Criteria

Inclusion:

- Subjects ages 6 to 21 who have loss of smell (anosmia) or dysosmia (disordered smell perception) and thought to have occurred due to COVID-19.
- Subjects who are able to complete the smell test (UPSIT), self-report their loss of smell, and do the assigned daily therapy.

Exclusion:

- Duration of anosmia or dysosmia <60 days
- Previous smell retraining
- Prior interventions for loss of smell (excluding those on Flonase and Azelastine)
- Contraindications for nasal budesonide treatment, as determined by the treating physician
- Active cigarette smoker or use of vapes
- Previous head trauma
- Congenital anosmia
- History of brain tumor
- Neurocognitive disorders
- Multiple sclerosis
- Seizure disorder
- Cystic fibrosis
- Primary Ciliary Dyskinesia
- History of nasal polyps
- Inability to self-report

Statistical Analysis Plan

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Study Outcomes

Survey responses from Smell Diary
UPSIT test results
SNOT-22 survey responses

Sample Size Calculation

There are no previous studies to base the power analysis on for pediatric patients. However, in adults, Nguyen and Patel (2018) found that 43.9% of those in the budesonide irrigation + smell retraining group experienced clinically significant (change in total score of at least 5) improvement on the UPSIT compared with 26.9% in the saline irrigation + smell retraining group. With alpha=0.05, power=0.80, and delta=0.179, a total of 222 subjects (111 in each group) would be required. However, we expect that we will detect a significant improvement in smell at 8 weeks compared with the initial visit, in both groups, with much smaller numbers. In addition, with the advent of vaccine approval for children ages 12-17, we do not expect to be able to enroll more than 60 subjects.

Analyses

Stata/SE version 16.1 will be used for all statistical analysis.
P value < .05 will be used for statistical significance.

Primary Outcome
The primary outcome measure 'Change in University of Pennsylvania Smell Identification Test (UPSIT) Score From Baseline to First Follow-up' will be analyzed with paired t-tests or Wilcoxon signed-rank test depending on the normality of the data. Mean and standard deviations will be reported for normally distributed data and median and interquartile range will be reported for non-normally distributed data.

Secondary Outcome
The secondary outcome measures 'Change in Sino-nasal Outcome Test-22 (SNOT-22) Score From Baseline to First Follow-up,' 'Change in Loss of Smell Question Score From Baseline to First Follow-up,' 'Change in University of Pennsylvania Smell Identification Test (UPSIT) Score From Baseline to 6 Month Follow-up,' 'Change in Sino-nasal Outcome Test-22 (SNOT-

22) Score From Baseline to 6 Month Follow-up', 'Change in University of Pennsylvania Smell Identification Test (UPSIT) Score From Baseline to 12 Month Follow-up,' and 'Change in Sino-nasal Outcome Test-22 (SNOT-22) Score From Baseline to 12 Month Follow-up' will be analyzed with paired t-tests or Wilcoxon signed-rank test depending on the normality of the data. Means and standard deviations will be reported for normally distributed data and medians and interquartile ranges will be reported for non-normally distributed data.

Cross-Over
Whether or not budesonide was added to smell retraining at or after the 8–12-week follow-up visit will be recorded. Outcomes at 6 months may be analyzed separately for those who were initially randomized to smell retraining only within the two subgroups 1) those who continued with smell retraining only and 2) those who crossed over to smell retraining + Budesonide, if sample size is sufficient for separate statistical analysis.

Analysis Inclusion
Only those who completed the 8–12-week follow-up will be included in the final analysis of these outcome measures.

Missing Data
Data imputation will not be used for missing data.

Harms

Serious adverse events and adverse events will be collected until completion of the participant's last study visit, for a maximum of 12 months following visit 1.