Acupuncture Therapy for COVID-Related Olfactory Loss

NCT04952389

March 23, 2021

IRB Minimal Risk Protocol Template

General Study Information

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Study Title: Acupuncture Therapy for COVID-Related Olfactory Loss

Protocol version number and date: Version 1 – March 23rd, 2021

Research Question and Aims

Hypothesis: There will be no difference in improvement in olfaction in patients with COVID-related olfactory loss treated with acupuncture, steroid rinses, and olfactory retraining compared to those treated with steroid rinses and olfactory retraining.

Aims, purpose, or objectives:

Aim 1: Describe the incidence of COVID-related olfactory loss.
Aim 2: Compare the effectiveness of acupuncture, steroid rinses, and olfactory training versus steroid rinses and olfactory training in the treatment of COVID-related olfactory loss.
Aim 3: Recommend a treatment paradigm for patients with COVID-related olfactory loss.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

Soon after the start of the COVID-19 pandemic, olfactory loss was identified as a common presenting symptom with anosmia reported in up to 75% of patients who tested positive for COVID-19 infection.[1] The severity of alteration of the sense of smell or taste is mild to moderate in about two thirds of patients with COVID-19 infection[2] and complete recovery is seen in 64% of patients after symptom onset.[3] In contrast, only 46% of patients with post-viral anosmia prior to the COVID-19 pandemic demonstrated clinically significant improvement in olfaction.[4] The improved recovery rate seen in COVID-19 associated olfactory loss may be explained by the selective sparing of the olfactory sensory neurons, which lack the ACE2 receptor.[5]

Olfactory training is the recommended treatment of post-viral olfactory dysfunction.[6] Typical treatment includes exposure to four intense odors twice daily for twenty seconds each.[7] Literature also supports the use of twice daily budesonide rinses in the treatment of olfactory dysfunction, with significant improvement seen in patients treated with budesonide irrigations and olfactory training compared to olfactory training alone.[8] Evidence supporting the use of systemic steroids is equivocal with one randomized trial showing no statistically significant improvement in odor detection threshold in patients with posttraumatic anosmia.[9] Few studies have investigated the use of acupuncture in the treatment of post-viral olfactory dysfunction with one randomized

trial demonstrating significant improvement in olfactory function compared to controls.[10] Acupuncture is a low risk intervention when performed by trained professionals. The risk of a serious adverse event is rare and below that of many common medical interventions. The occurrence of serious adverse events following acupuncture treatment is extremely rare when the acupuncture treatment is performed by a skilled and trained provider. Prospective studies of more than one million acupuncture treatments found that the risk of a serious adverse event is estimated to be 0.05 per 10,000 treatments and 0.55 per 10,000 individual patients.[11] Acupuncture is generally safe for patients taking anticoagulant medications. A retrospective chart review found the occurrence rate of microbleeding (stopped within 30 s) was <4.8%.[12] Additionally, acupuncture during pregnancy appears to be associated with few AEs (adverse events) when correctly applied.[13]

Limited data is available regarding the treatment of COVID-19 associated olfactory dysfunction. The standard of care for olfactory dysfunction at our institution is olfactory retraining and twice daily budesonide rinses. The current study is designed to investigate the role of acupuncture in the treatment of post-viral olfactory dysfunction, specifically related to COVID-19 infection. By doing so, we hope to develop a treatment algorithm for COVID-19 related olfactory dysfunction that can be applied to clinical practice.

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2. Borsetto D, Hopkins C, Philips V, et al. Self-reported alteration of sense of smell or taste in patients with COVID-19: a systematic review and meta-analysis on 3563 patients. *Rhinology.* 2020;58(5):430-6.
3. Chary E, Carsuzaa F, Trijolet JP, et al. Prevalence and recovery from olfactory and gustatory dysfunctions in Covid-19 infection: a prospective multicenter study. *Am J Rhinol Allergy.* 2020;34(5):686-93.
4. Cavazzana A, Larsson M, Münch M, Hähner A, Hummel T. Postinfectious olfactory loss: a retrospective study on 791 patients. *Laryngoscope*. 2018;128(1):10-5.
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7. Kattar N, Do TM, Unis GD, Migneron MR, Thomas AJ, McCoul ED. Olfactory training for postviral olfactory dysfunction: systematic review and meta-analysis. *Otolaryngol Head Neck Surg.* 2021;164(2):244-54.
8. Nguyen TP, Patel ZM. Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss. *Int Forum Allergy Rhinol.* 2018;8(9):977-81.
9. Yan CH, Overdevest JB, Patel ZM. Therapeutic use of steroids in non-chronic rhinosinusitis olfactory dysfunction: a systematic evidence-based review with recommendations. *Int Forum Allergy Rhinol.* 2019;9(2):165-76.
10. Dai Q, Pang Z, Yu H. Recovery of olfactory function in postviral olfactory dysfunction patients after acupuncture treatment. *Evid Based Complement Alternat Med.* 2016;4986034.
11. White A. A cumulative review of the range and incidence of significant adverse events associated with acupuncture. *Acupunct Med.* 2004;22(3):122-33. doi: 10.1136/aim.22.3.122. PMID: 15551936.
12. Kim YJ, Kim SK, Cho SY, et al. Safety of acupuncture treatments for patients taking warfarin or antiplatelet medications: Retrospective chart review study. *European Journal of Integrative Medicine* 2014;6(4): 492-6. https://doi.org/10.1016/j.eujim.2014.04.004.

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Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol.*

This study will be a prospective randomized controlled trial and will include subjects who present to the ENT clinics previously diagnosed with post-viral olfactory dysfunction secondary to COVID-19 infection and add newly diagnosed subjects in the future. All patients with post-viral olfactory dysfunction of at least 4 weeks and a positive COVID PCR will be eligible to participate in the study. This study has received approval by the COVID-19 Research Task Force. Interested patients can complete the COVID-19 research interest form posted on an externally-facing Mayo Clinic COVID-19 Research website and will be directed for enrollment by the COVID-19 Research Clearinghouse staff if eligible. The Mayo social media accounts will also include recruitment phrases such as "If you have loss of sense of smell and a history of COVID-19 infection, then consider seeing our Rhinology team for treatment options" and "If you have an appointment in the Mayo Clinic ENT department and have a history of COVID-19 infection, your provider may ask you about loss of sense of smell and participation in a study looking at treatment options."

Phone, virtual, or in-person consents may be obtained by enrolling patients who are being seen by an ENT specialist at Mayo Clinic, or who previously saw a Mayo specialist who diagnosed them with olfactory loss from COVID-19 infection. For patients seen virtually, the following screening questions will be asked:

- "Do you have purulent (colored or foul smelling) nasal or postnasal drainage?"
- "Do you have worsening nasal obstruction over the past 6 months?"
- "Do you use a steroid (budesonide or mometasone) nasal irrigation daily to treat chronic rhinosinusitis?"
- "Have you been treated with an antibiotic for a sinus infection in the past 3 months?"

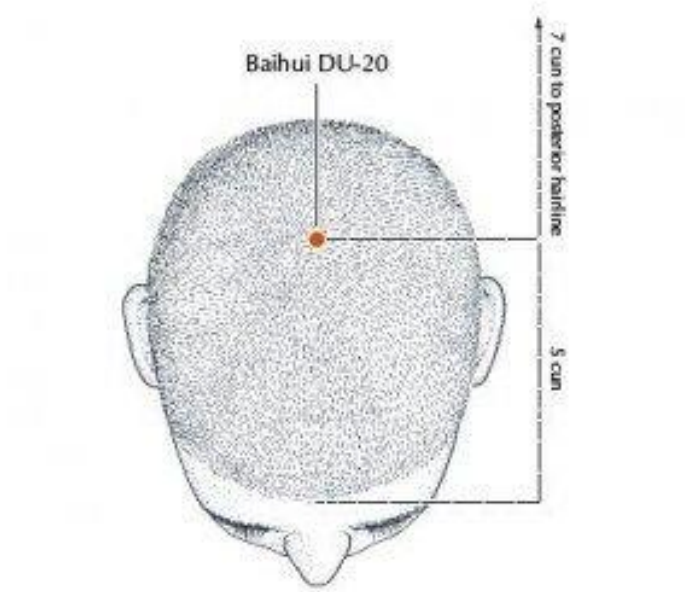
If any of the above screening questions are positive, we would recommend an in-person appointment to rule out other causes of olfactory loss prior to treatment or enrollment in the study. If the patient does decide to be seen in person in the ENT department and it is determined by their provider that their olfactory loss is due to COVID-19 infection, they would then be approached about enrolling in the study. This in-person appointment would be billed to the patient or his/her insurance, as normal. Patients who are seen via telemedicine with a negative screening will be offered enrollment in the study provided they are willing to travel to Mayo if selected into the treatment arm.

Enrolled patients will be randomized into two groups at the time of accrual. The first group will undergo ten sessions of acupuncture therapy with a licensed acupuncturist, in addition to the twice daily budesonide irrigations and olfactory training. Mayo Clinic compounding pharmacy formulates a powdered version of budesonide that comes in capsules. We will mail it to patients who are not seen in person along with instructions on how to perform the nasal irrigations in person or electronically. The clinic nurse will also review the instructions with the patient during the in person or virtual visit. Acupuncture therapy will consist of two treatments per week for five weeks. Acupuncture points will include Du-20, Du-23, Li-20, Li-4, Lu-7, and St-36 (see diagrams below of acupuncture points). There is one point, Li-4, which is contraindicated for pregnant patients because it is known to induce labor. This point will be avoided in all pregnant women randomized to acupuncture but will be used in everyone else. Needles will be left in place for 25 minutes per session. The second group will be treated only with twice daily budesonide rinses and olfactory training, which is considered

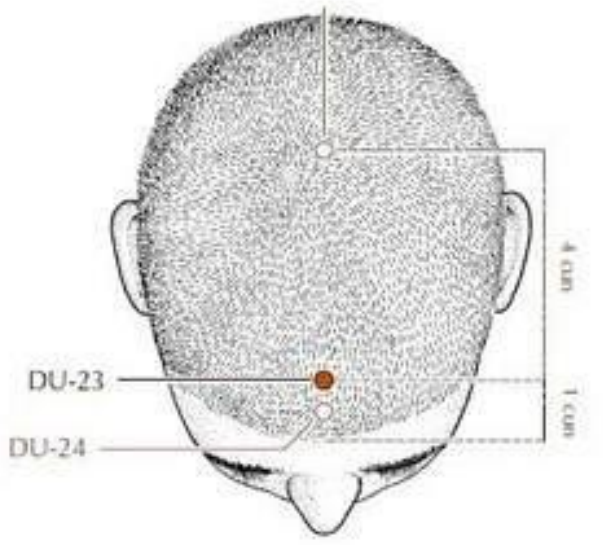
the standard of care. Patients can opt out of the study at any point. UPSIT will be used to assess the sense of smell at the initial visit and after three months of treatment. A clinically significant difference in UPSIT score is defined as a change in total score of 5 points.[8] This is a scratch-and-sniff test where patients are given four multiple choice options to choose the correct answer to each scented box. The initial test will be mailed to the participant if consent is obtained by telemedicine appointment. If consent is obtained in person, the test may be delivered to the participant at the time of the appointment or mailed. The 3-month test will be mailed to all participants unless they are returning for follow-up at that time. If the UPSIT test is conducted remotely, we will provide verbal instructions during the initial telemedicine appointment on how to complete this. There are also instructions included in the test packet that is mailed to the patient instructing the patient to scratch, sniff, and fill in the corresponding multiple-choice bubble with the included pencil.

Subjective measures of olfactory loss and sense of smell will also be obtained at the initial visit (virtual or in-person) and at 3 months using the SNOT-22 questionnaire and 10-point visual analog scale with 0 representing no sense of smell and 10 representing normal smell. Both of these documents may be mailed to patients. Results will be analyzed based on original treatment group. We will also perform subgroup analysis for age, gender, and duration of olfactory loss of 1-4 months, 4-8 months, 8-12 months, and greater than 12 months.

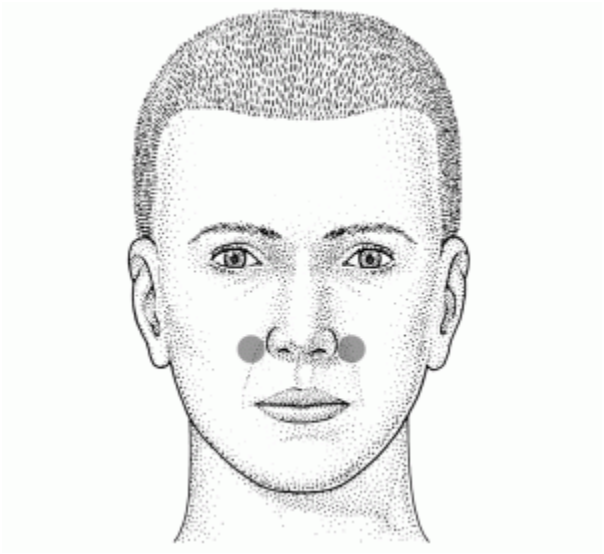
Acupuncture Point Locations for Anosmia



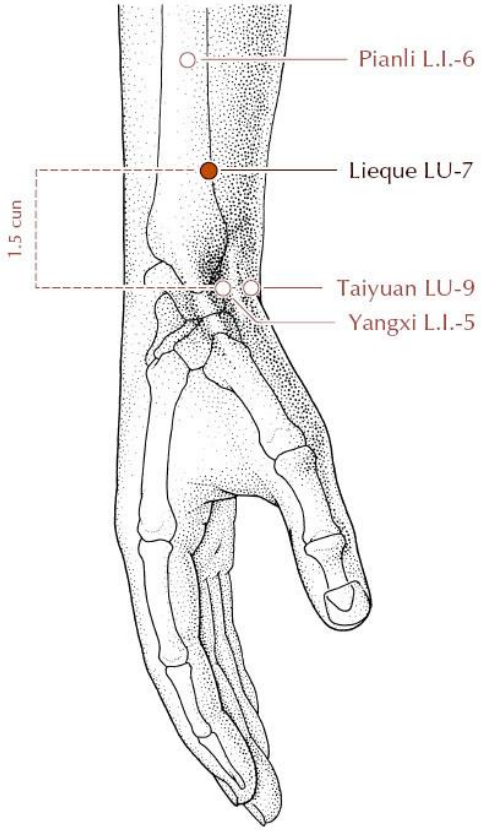
Du-20 is located at the top of the head.



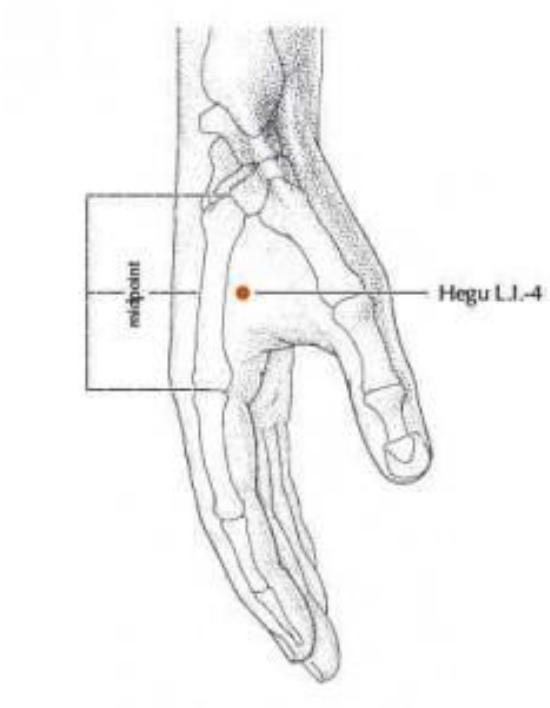
Du-23 is located approximately 1cm above the hairline.



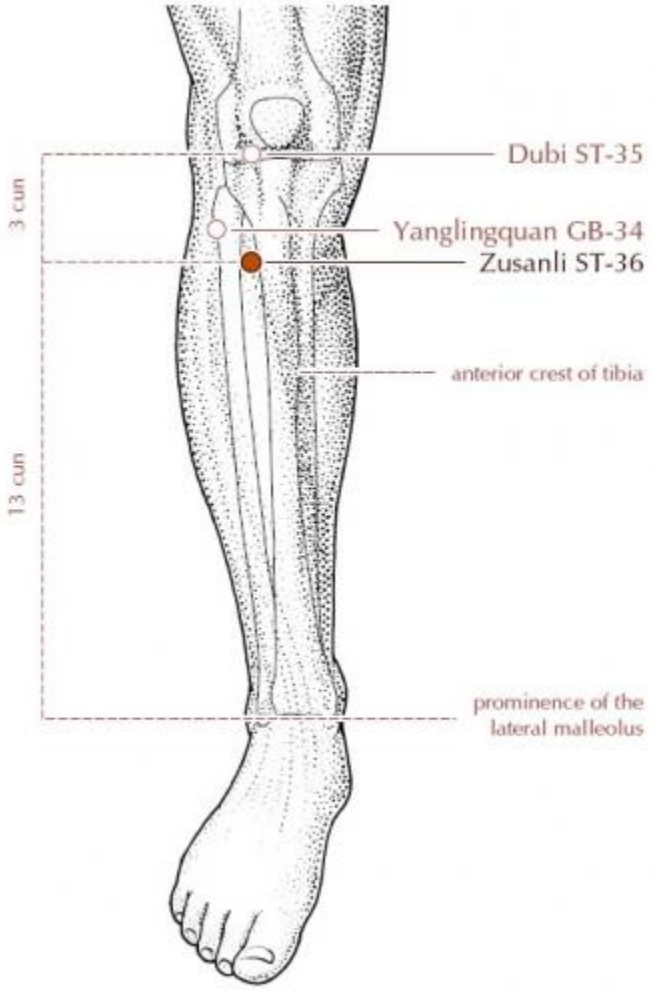
Li-20 is located at the nasolabial groove.



Lu-7 is located 1.5 inches above the crease of the wrist along the radius.



Li-4 is located on the dorsal side of the hand between the thumb and index finger.



St-36 is located 3 inches below the knee on the lateral side of the tibia.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 100 patients

Subject population (children, adults, groups): Adults

Inclusion Criteria: 18 years or older, including pregnant/breastfeeding women. Acupuncture is safe before, during, and after pregnancy and is associated with few adverse events when correctly applied.[13] Additionally, patients must have post-viral olfactory dysfunction > 4 weeks and a history of positive COVID-19 PCR.

Exclusion Criteria: Less than 18 years of age; active sinus infection, new diagnosis of untreated CRS, prior diagnosis of dementia or Parkinson's, prior head trauma or neurosurgical procedure resulting in olfactory loss, patients who do not speak or read English, patients unable to understand and sign the study consent

Biospecimens

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☒ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement:
This is novel work so estimates for change in UPSIT score for the 2 groups are unavailable. Therefore, no power/sample size calculation is possible.

Data Analysis Plan:
Differences in demographic/history/clinic factors between groups to be compared will be analyzed using chi-square or fisher's exact as appropriate for categorical factors and Wilcoxon rank sum test for continuous factors.

Analysis of Covariance (ANCOVA) will be used to model differences in change in UPSIT score from baseline between the case and control group while accounting, where able, for any demographic/historical/clinical factors that are found to be significantly associated with UPSIT score.

Endpoints
Primary: Post-treatment UPSIT scores
Secondary: Patient-reported subjective olfactory loss