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STIMULATION OF THE LINGUAL NERVE FOR INCREASED SALIVA OUTPUT

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ABSTRACT

Xerostomia is the perception of oral dryness. In addition to discomfort, xerostomia can lead to several long-term medical complications within the oral cavity and gastrointestinal system. Treatment options are limited and are either not effective or not convenient for all people with xerostomia. In this study, we designed, tested, and further developed an oral mouth guard insert with electrodes for stimulating the lingual nerve on the medial side of the lower jawbone. Saliva production, collected in the context of randomized on/off testing with a subject blinded to the test condition, resulted in significantly more saliva output during and following lingual stimulation (2.07 g over one minute) versus off stimulation control conditions (1.58 g also over one minute) (two-sample t-test, p=0.001). The proof-of-concept prototype is poised for further refinement with system integration and improvement in packaging. Xerostomia is a common medical condition, and non-implantable devices that can increase salivation on-demand hold significant promise for treating xerostomia in the broader public.

Keywords: Xerostomia, Stimulation, Salivation

1. INTRODUCTION

Xerostomia, known broadly as dry mouth, is the perception of a lack of saliva within the oral cavity. Usually, this symptom is driven by under-producing salivary glands but can also result from abnormal sensory and autonomic neural activity. Typical causes of xerostomia include medications (for example, anticholinergics, antidepressants, opioids, and benzodiazepines, antipsychotics), Sjogren's syndrome, nerve damage, as well as radiation and chemotherapy of the neck and face. In many cases, xerostomia leads to further medical complications that can deteriorate oral, gastrointestinal, and mental health.

Sufficient saliva output is required for good oral health. Without enough saliva, proper digestion, speech, infection control, and teeth and gum health decline. Although, xerostomia as a symptom is subjective, Billings et al.[1] determined that 18.1% of females and 24.0% of males in a convenience population (n=710), ages 19-88, suffer from xerostomia based on saliva flow rates. Additionally, meta-analysis has shown that dry mouth tends to be an age correlated syndrome, with 29-57% of older persons experience xerostomia [2]. Unfortunately, treatment options are somewhat limited.

Xerostomia symptoms can fluctuate throughout the day depending on the underlying cause. Treatments include artificial moisturizers, saliva flow stimulating chewing gum, medications (with other side effects), and some nerve stimulation devices. Many complaints have risen regarding current treatments for xerostomia. Among them are short lasting results, poor results, constant hands-on administration, and uncomfortable side effects. Improved treatment options are needed.

Some technologies have sought to control salivary gland output by interfacing with the parasympathetic nervous system. Ami et al. [3] showed, using a crown implanted stimulator, improvements in saliva output and patient perception of oral dryness. The challenge to this potential product is that it requires dental implantation. The same company (Saliwell) also has a commercially available handheld electrostimulation system to manually stimulate the nerves projecting to the salivary glands. This product requires the user to place a large tuning fork device with bilateral electrodes within the oral cavity and hold them still throughout the therapy. To address these user challenges, we developed a non-implantable nerve stimulator device that enables user-specific control over placement of the electrodes to achieve robust saliva output through stimulation of the lingual nerve.

2. MATERIALS AND METHODS

Stimulation was delivered with an S88X Stimulator (Grass Instruments) and through a lead of cylindrical electrodes (1.5 mm height, 1.3 mm diameter, per electrode). For the initial prototype, the lead was held in place by means of a mouth guard and adjustable fixturing system that controlled the position of the lead device (Fig. 1). The lingual nerve runs parallel to the adjacent lower jawbone and below the molars (Fig. 2), but varies in exact location and angle from individual to individual. Electrode position was determined for an individual test subject based on which positions made them subjectively feel increased salivation. Lead angle was identified by moving the fixturing arms up and down to change electrode position relative to the lower jawbone. Electrode depth was found by moving the electrode in and out of fixturing arm loops. Angle and depth adjustments were implemented based on subjective feedback before beginning further experiments. With the mouth guard fixture placed over the molars and holding the electrode on the

gums proximal to the lingual nerve, the stimulation experiment was conducted to assess saliva output.

Saliva samples were collected for one subject with the stimulation settings randomized and the subject blinded to the testing conditions. Two settings were tested each a total of 15 times: (1) control with no stimulation; and (2) electrical stimulation through a bipolar pair of electrodes. In the latter case, the stimulator delivered biphasic pulses at 5 Hz with each pulse phase having a 1 ms duration and amplitude of 6 V. During the unstimulated setting, the fixture and electrodes were in place without any electrical output. After 1 minute in either test condition, the subject then removed the mouth guard and emptied as much saliva as possible over the subsequent minute from the floor of the oral cavity. During the tests, the subject was instructed to minimize mechanical tongue movement, which may inadvertently modulate saliva output. Following the sample collection, a final minute was used as a rest period between testing conditions. During the break period a simple question was asked: Did the subject perceive an increase in saliva output? The answer options were yes, no, or maybe. The process was then repeated for the remaining samples.

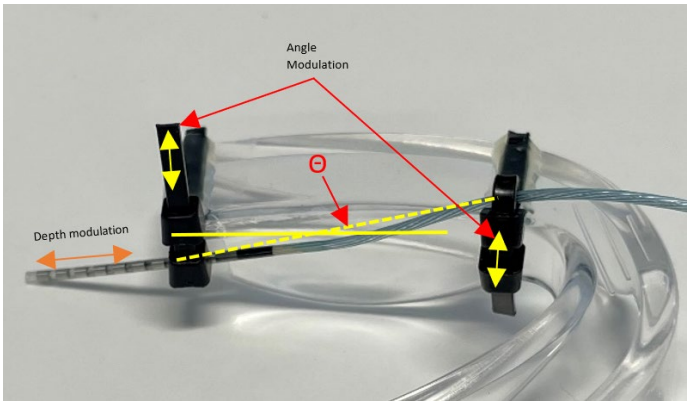

FIGURE 1: INITIAL FIXTURING SYSTEM PROTOTYPE FOR CONTROLLING PLACEMENT OF A LEAD OF ELECTRODES WITHIN THE ORAL CAVITY. SHOWN ARE DIFFERENT WAYS TO TRANSLATE AND ROTATE THE ELECTRODE POSITIONS. IN ORANGE, THE ROSTRAL-CAUDAL DEPTH OF THE ELECTRODE. IN YELLOW, THE TWO DORSAL-VENTRAL ADJUSTMENTS, WHICH ALSO CHANGED THE ANGLE RELATIVE TO THE JAW LINE.

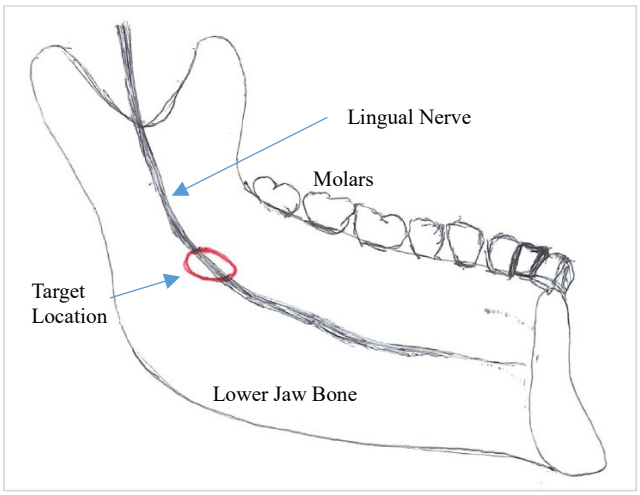

FIGURE 2: THE LINGUAL NERVE RUNS ALONG THE MEDIAL SIDE OF THE JAW BONE BELOW THE MOLARS. THE THICKEST PART OF THE NERVE IS POSITIONED DISTAL IN THE ORAL CAVITY. THE TARGET LOCATION WAS CHOSEN TO BE NEAR THE DISTAL MOLAR.

The sum of the saliva weight for each test condition was analyzed using a two-sample t-test in Minitab Statistical Software. The t-test settings were 95% confidence, difference ≠ hypothesized difference, and 15 total samples of each setting.

3. RESULTS AND DISCUSSION

The fixture design prototype held the electrodes in place, but some manual manipulation was required to push the electrodes against the target location. Once the electrodes were positioned where the subject felt saliva output, the configuration was used for the remainder of the study. The configuration, although specific to this subject in this study, was 7 mm back from and 12 mm below the rear adjustment point. The front adjustment point held the lead 8 mm above the top of the mouth guard.

Data collected (Fig. 3 & 4) showed some overlap but a clear distinction between the two data populations. The stimulated data population was statistically different from the control group ($p = 0.001$), thus rejecting the null hypothesis, meaning the groups were statistically different. The lowest value in the stimulation data population (1.20g) fell 0.42g lower than the mean value of the normal data. After reviewing subject feedback data for each data point, it was found that the subject did not feel output during this stimulation round. It could be possible that the electrode was not interfacing in the same location for this sample. In addition to the outlier, overlap can be seen in the two data sets. During the testing additional subjective feedback was provided whether they felt saliva continue to flow after a round of stimulation. This could possibly lead to increased saliva output during control periods.

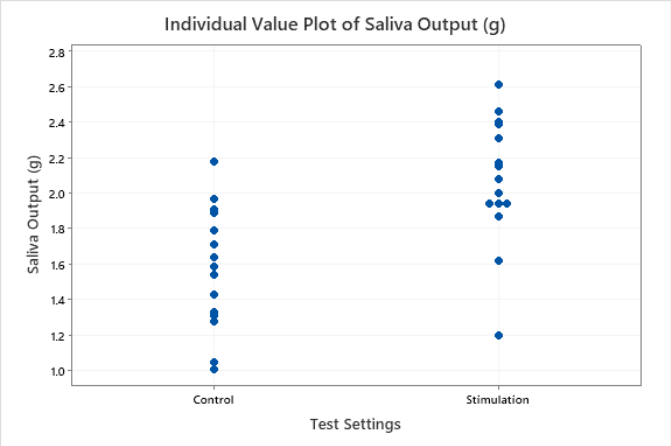

FIGURE 3: SHOWN IS AN INDIVIDUAL VALUE PLOT OF SALIVA OUTPUT DATA FOR THE CONTROL AND STIMULATION POPULATIONS.

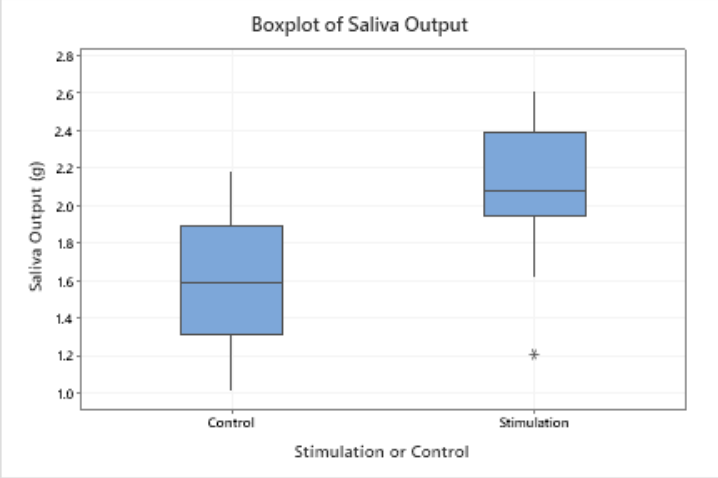

FIGURE 4: SHOWN IS A BOX PLOT OF SALIVA OUTPUT DATA FOR THE CONTROL AND STIMULATION POPULATIONS.

The feedback from the subject (Fig. 5) shows, although the study was blind, the subject identified saliva output as a maybe or yes when the stimulation was on 14 out of 15 times. Additional feedback was given that saliva secretion seemed to occur towards the soft palate of the oral cavity despite targeting the inferior lingual nerve along the lower jawbone. This suggests that the effects of stimulation may not only be activating efferent parasympathetic nerves, but also engaging neural reflex pathways. During no stimulation runs, 13 out of 15 runs were identified as no increase in saliva output. No side effects were perceived.

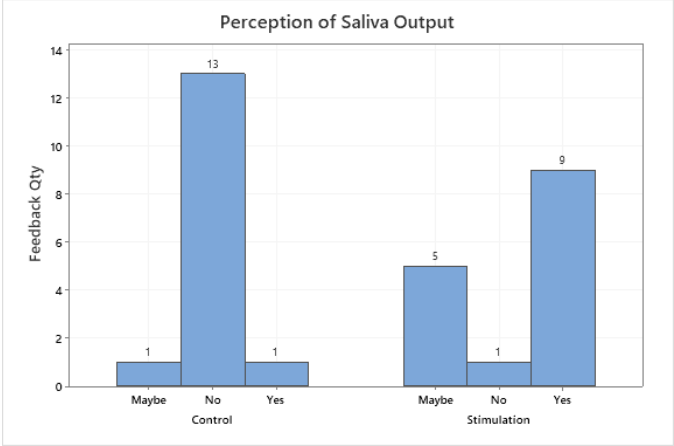

FIGURE 5: A SIMPLE QUESTIONNAIRE WAS ADMINISTERED DURING THE BREAK BETWEEN EACH CONFIGURATION TESTED. THE QUESTION ASKED IF SALIVA OUTPUT WAS FELT WITH RESPONSES OF MAYBE, NO, OR YES.

Although the fixture design improved the subject's ability to hold electrodes in a repeatable location, the intent of the design was to completely reduce manually manipulating electrodes. This was considered for the second prototype as shown in Figure 6 where the electrode arms were angled inwards. Among a tighter buccal wall interface, the design also eliminates the bulky electrode used for the feasibility study. In its place, the integrated systems design includes the electrodes, controlling circuit, and battery mounted to or within a custom fit mouth guard. To improve user experience, the electrode angle and x/y positioning in the mouth for a custom fit on all anatomical variation. Additionally, an on/off switch in the form of a tongue-controlled push button is included for users to easily control therapy. This second-generate design will reduce variation in the interface between the electrodes and the lingual nerve target location.

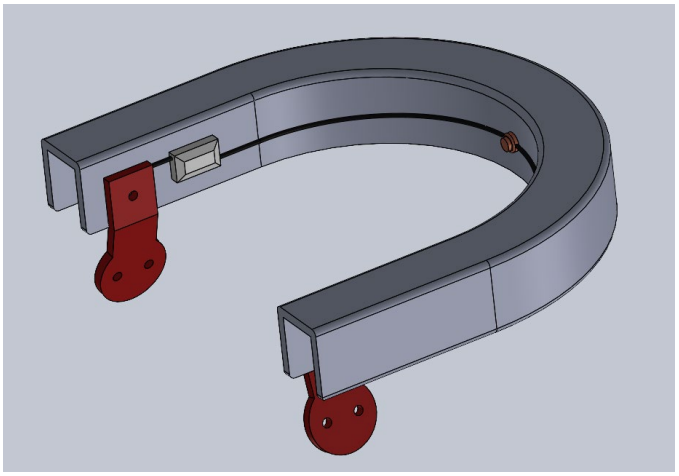

FIGURE 7: SHOWN IS THE PLANNED NEXT REVISION INCLUDING ELECTRODE POSITIONS MODULATION,

CIRCUITRY HOUSING, AND A TONGUE PUSH BUTTON FOR ACTIVATION.

This study showed a statistically significant difference between lingual stimulation versus a no stimulation control in terms of quantitative weight of saliva output. There are several considerations to consider in terms of the test methods with the goal of reducing variation for future studies. One possible improvement would be increasing the wash-out times between tests. Doing this should reduce potential confounding data between stimulation periods and no stimulation periods by eliminating the saliva secretion carryover from a stimulation to a no stimulation data point.

In addition to study improvements, expanding the study will be needed to better understand the devices efficacy across a cohort. Ideally, adding a variety of ages, genders, and medical backgrounds would provide a sufficient picture of the device's performance. Collecting a baseline saliva output without the device in place will also provide a clearer picture of the amount of mechanical stimulation that the device contributes to saliva output. Further, a more comprehensive questionnaire to capture the subjective user feedback will be administered to improve the design of the system.

A review into the lingual track would suggest there may be potential side effects relating to the tongue. First, the lingual nerve innervates the anterior two-thirds of the tongue for taste. Therefore, false taste or loss of taste may be perceived by a subject. Second, the lingual nerve provides sensation to the tongue so tingling or numbness may be perceived, although in this study, the subject did not report any of these side effects. Further study in larger subject numbers to determine how these potential side effects may manifest given anatomical variability within the general population.

4. CONCLUSION

Non-invasive electrical stimulation of the lingual nerve was shown to increase saliva output in one subject using pair of electrodes anchored to a mouthguard. The device provided two levels of adjustment to ensure that the electric field could be positioned and aligned to the nerve to achieve robust and statistically significant increases in salivary output. Such devices have potential benefit to individuals with xerostomia.

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