Collagen Crosslinking Agent Injections to Reduce Soft Palate Vibrations in Equine Snoring

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Statement of Purpose: Snoring is a sleep cycle disruption affecting 19-48% of men and 14-34% of women in the United States [1]. Occasionally, snoring can lead to obstructive sleep apnea syndrome, or OSAS, where obstruction of the airway interrupts normal breathing. OSAS, affecting about 28% of men and 24% of women over age 65, can lead to various respiratory or cardiovascular problems, such as high blood pressure, stroke, heart failure, diabetes, and depression. Overall, 56-75% of snoring and OSAS cases are directly related to weakening of the soft palate. Severe snoring weakens the soft palate because of its high energy, low frequency vibrations. Current treatments for snoring and OSAS involve over the counter nasal strips, non-surgical CPAP machines, or various surgeries. NEXT, or Nonsurgical Exogenous crosslink Therapy, is a potential new treatment for snoring and OSAS. In its present form, it is a genipin-based injectable reagent that reduces high energy deflections of the soft palate by crosslinking the native collagenous matrix to reduce tissue compliance.

Methods: An equine model was used to test the NEXT reagent for efficacy and safety in treating OSAS because horses experience an awake form of snoring during exercise, called dorsal displacement of the soft palate, or DDSP. Like human snoring, DDSP is characterized by high-energy snores that weaken the soft palate and disrupt normal breathing. To test the efficacy of NEXT, equine soft palates were tested in a wind tunnel to determine the deflection and vibration frequencies of control and treated soft palates. The treated soft palates were either soaked in a buffered 0.33% genipin solution or injected in two locations with 1 ml of 40mM, 100mM or 150mM of buffered genipin solution. They were then secured in the wind tunnel device and tested at 14 m/s in transient and steady state conditions to mimic equine exhalation. A laser micrometer on an XY system was used to measure the deformation, ΔZ, in nine locations on the soft palate. To test the safety and efficacy of the NEXT treatment strategy, an equine in vivo study was completed using six horses: three controls and three diagnosed with DDSP. The soft palates were injected with 1 ml of 100 mM buffered genipin solution in two locations using a transnasal endoscope. All six horses were then closely monitored for seven days. On day eight, the three control horses were sacrificed, and their soft palates were harvested for histological analysis. The three DDSP horses underwent pre injection and post injection dynamic endoscopes and auditory breathing recordings to quantify the frequency and amplitude of DDSP snoring.

Results: Overall, the wind tunnel results had an increase in steady state frequency and a decrease in soft palate deflections. Untreated soft palates had low frequency, high amplitude vibrations which increased flapping. Treated soft palates had low amplitude, high frequency vibrations which decreased flapping. The 100mM injected soft palates demonstrated similar reduction in deflections compared to the higher concentration treatments, making it the preferred concentration for the in vivo study. In the in vivo study, all six horses were successfully treated with two 1 ml trans-nasal injections of 100mM buffered genipin into the soft palate. None of the horses experienced any distress or abnormal effects for the seven days post treatment. Preliminary audio recording data results analyzed using Matlab showed general reduction in DDSP snoring occurrences. Pre injection recordings in the time domain had strong snoring amplitude peaks followed by gaps with no breathing. In the post injection recordings, the amplitude peaks were lower and the breathing rhythm was steady without any gaps. In the frequency domain, pre injection recordings had high amplitude peaks for all frequencies. Post injection recordings showed a large decrease in amplitude for higher frequency sound vibrations and a slight reduction in amplitude for lower frequencies. Early post injection dynamic endoscope results diagnosed one horse with intermittent DDSP, another horse without DDSP, and the final horse has yet to be tested. Histological analyses of the control horse soft palates are pending.

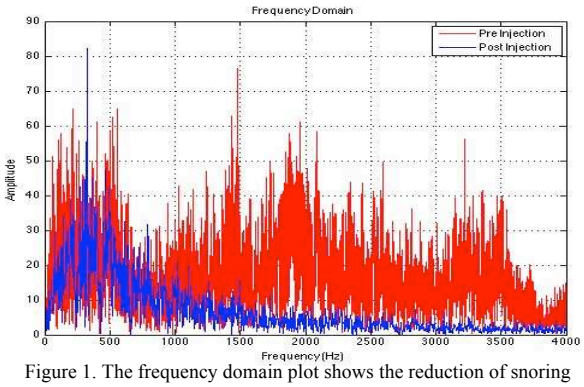

Figure 1. The frequency domain plot shows the reduction of snoring amplitude after injection of the soft palate with the NEXT treatment.

Conclusions: Based on the wind tunnel data, the NEXT treatment using a buffered genipin reagent was able to reduce the deflections and vibrations of the soft palate. The audio recordings results from the in vivo study supported the wind tunnel results with a decrease in amplitude at high frequencies of the soft palate during snoring. However, the audio results did show a reduction in amplitude in the low frequency range, which could be due to low frequency background noise, such as exercise wind, that was encountered during the audio recordings. Additionally, the in vivo study completely cured DDSP for at least one of the three horses, supporting the efficacy of the NEXT product to prevent soft palate displacements. Potential future projects include DDSP equine studies to further analyze the efficacy of NEXT. The ultimate goal would be to apply this study to human soft palates for snoring and sleep apnea applications.

References: [1] Ram S, Seirawan H, Kumar SK et al. Prevalence and impact of sleep disorders and sleep habits in the United States. Sleep Breath. 2010;14:63-70.