TITLE: MULTI-LEVEL UPPER AIRWAY IMPLANTS FOR TREATMENT OF OBSTRUCTIVE SLEEP APNEA: TOLERANCE IN CANINES AND FINITE ELEMENT ANALYSIS.

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common medical condition with an estimated prevalence rate of 3-7% in the general population, with some ethnic variation. OSA is associated with considerable morbidity including cardiovascular disease, stroke, daytime sleepiness, motor vehicle accidents, insulin resistance, obesity, neurocognitive deficits and overall diminished quality of life. The majority of airway collapse in OSA is thought to occur at two levels in the upper airway; the soft palate and base of tongue. Although continuous positive airway pressure (CPAP), the most widely used therapy for OSA, is effective, patient adherence rates are poor and are estimated to be as low as 40 percent. Thus new approaches for maintaining airway patency are needed to improve outcomes in patients with OSA. The objective of our research was to examine clinical and histologic outcomes of a novel, minimally invasive surgical implant developed for OSA in a canine model, and to model the implant a computer generated airway model via Finite Element Analysis.

MATERIALS AND METHODS

DEVICE: The implant (Figure 1) is a silicone elastomer with non-woven polyester fabric-reinforced loops located on each end that are designed to enhance tissue attachment. Implant position can be visualized with the 90% Platinum/10% Iridium marker bands. The device is maintained in a stretched position pre-implantation by bioabsorbable polymer coils. Following implantation, the bioabsorbable polymer undergoes gradual resorption in parallel to native tissue ingrowth through the reinforced loops at each end. Upon complete polymer resorption, there is an approximate 33% shortening of the original implant length.

PRE-CLINICAL STUDY: This study was performed in a facility registered with the United States Department of Agriculture to conduct laboratory animal research, and the study was approved by an Institutional Animal Care and Use Committee. Physical exams were performed on study animals prior to release from quarantine. To evaluate performance and local tissue response of the implant, a total of 18 male and female mongrel dogs, >22 kg and with suitable anatomy, were selected. Pre-operatively, canines were administered cefazolin for infection prophylaxis, acepromazine and propofol for anesthesia, and buprenorphine for analgesia. There were four implants per canine in almost all cases. Two implants were placed extending from the junction of the hard and soft palate vertically toward the inferior end of the soft palate, 0.5 cm to the left and right of the midline; two implants were placed into the right and left sides of the tongue, oriented in the sagittal plane within 1 cm of the midline. Animals received a fixed formula diet certified by the manufacturer regarding nutritional components and environmental contaminants. Tap water was provided *ad libitum.* Clinical Observations were completed daily, while fluoroscopy was completed at 2 and 4 weeks and then monthly to confirm and observe implant locations over time. Subgroup termination procedures were planned at 6 and 12 months, according to existing facility SOPs, and target organs were dissected, packaged and shipped to the histology-processing site along with complete chain of custody documentation.

HISTOLOGY: Canine tongue and palate samples were trimmed into serial sections for evaluation of the implant and surrounding tissues at the site of each attachment element and the middle elastic element. Two sections were taken perpendicular to the long axis of each element, processed and sectioned for review under light microscopy. Inflammation Grade was scored on a scale of 0-5: 0=none, 1=minimal, 2=mild, 3=moderate, 4=marked and 5=overt abscess

formation. Three scores were given for each implant; one for each attachment element end of the implant and one for the middle erodible element.

FEA Model: FEA is a widely-accepted numerical method for analyzing stresses and strains within structures and other physical problems such as those involving heat or fluid flow and electromagnetic systems. With accurate information describing the system such as material properties and loads, FEA models provide accurate representations and simulations of treatment outcomes. FEA models accomplish this by solving a set of equations representing the system in finite steps by dividing the physical representation into many small components or finite elements which can be more easily handled mathematically. FEA has been increasingly applied to biological systems, including muscular systems such as the heart and tongue. Three-dimensional biomechanical models of the tongue have been used in the study of speech motor control and tongue motion. This study incorporated the results of several studies. These studies clearly delineate the overlapping muscular structure, the range of motion, and the forces implied by the tongue and provide the foundation for the finite element model. [1,2,3]

Using the FEA model, several implant lengths, placement locations, and techniques were examined. In each case the implant was modeled as contracting by 30%. The material properties of the implant were set to represent the silicone 4830 material with a modulus near 2 N/ mm^2. The tongue was represented by non-linear components (Ogden parameters).

RESULTS

Canine Model: Sixty-six implants were completed with the lead design in 18 canines; 36 palate and 30 tongue. Four canines received single tongue implants and 1 received 2 tongue implants from an early design. There were 3 complications: missing palate implant at 3 weeks; exposed

palate implant at 10 months; abscessed tongue implant after 3.5 months in a device that had been difficult to insert and histological evaluation showed suppurative exudate as well as pockets of pyogranulomatous inflammation (Inflammation Grade 5). Each of the other 3 implants in these 3 canines and all of the implants in the other canines were well tolerated in the palate and tongue with normal behavior, swallowing, and oral intake without airway obstruction noted with up to 1 year of follow-up.

Five animals were euthanized at 6 months; two of these had previous removal of their tongue implants (at 4 months) to enable evaluation of the healing response. Eight palate implants from four canines were evaluated histologically at 6 months. The mean Inflammation Grade was 1.25 ± 0.53 for all elements combined, 1.18 ± 0.54 for the attachment elements and 1.37 ± 0.52 for the bioabsorbable elements. There was no outward radiating or dissecting fibrosis spreading beyond the immediate device capsule at any of the attachment element or erodible element sites, including the 1 with Grade 3 inflammation. (TABLE I)

Six tongue implants from three canines were evaluated at six months. The mean Inflammation Grade was 1.61 ± 0.92 for all elements combined, 1.67 ± 0.98 for the attachment elements and 1.50 ± 0.84 for the erodible elements reflecting minimal to mild inflammation. All but one of the six elastic elements had inflammation scores of 1 or 2 indicating good tolerance. One device had an Inflammation Grade of 3 due to increased chronic inflammation. (TABLE I) The two-month post-explant, tongue-healing response in two canines was excellent. The implant tissue previously surrounding the implants from those two canines were reviewed and scored. Of the 12 segments analyzed eight had no inflammation, 2 were Grade 1 and 2 were Grade 2. Figure 2 provides an illustration of the typical appearance of an implant with minimal, Grade 1 inflammatory response.

Two additional canines were euthanized at 12-months and the palate and tongue slides revealed a continued reduction in inflammation grades on microscopic evaluation. The eight palate segments had a mean grade of 0.67 ± 0.77; 0.75 ± 0.96 for the attachment elements and 0.63 ± 0.74 for the erodible elements. Similarly the mean grades for the tongue were 0.83 ± 0.72 for all elements, 1.14 ± 0.69 and 0.25 ± 0.50 for the attachment elements and erodible elements respectively reflecting excellent tissue response over time.

Finite Element Analysis

Figures 3, 4 and 5 demonstrate the dual level implant approach with FEA. The palate implant FEA predicts effective flexion of the soft palate anteriorly, away from the airway in Figure 3, while Figures 4 and 5 model the effective advancement of the tongue with single implant and double implants respectively with insertion from the submental position, and show the superior effect of a two-implant approach. Closure of the airway, either in the normal swallowing or in a pathologic state (apnea) requires only a few mm of motion of the region near the base of the tongue. For the implant to effectively function, its action needs to overcome a posterior displacement ranging from 5 to 8 mm. FEA shows that this range of counteracting motion is produced by the implant.

DISCUSSION

The extensive health consequences of OSA [4], the associated costs to the health care system [5,6] and the societal impact [7] have encouraged the pursuit of innovative solutions. There is a clear need for an OSA solution that can address patient compliance and provide a significant and lasting effect with minimal disruption of tissue. Our research endeavored to identify a safe and effective solution that would address airway obstruction at the levels of the soft palate and tongue

simultaneously. Utilizing materials with well characterized safety profiles in humans we developed a flexible implant suitable for both areas. The purpose of the tongue implant is to advance or prevent the collapse of the tongue to maintain patency of the airway. The purpose of the palate implant is to reposition the soft palate, thus preventing collapse of the airway. Histologic evaluation of canine tissues demonstrated excellent biocompatibility, with minimal fibrous response or inflammation of the tongue and palate at 6 and 12 months. Encapsulation of the implant ends demonstrated robust attachment. The attachment is necessary to provide the desired supportive mechanism of action, yet allows for flexibility of tongue during speech and swallowing.

The degree of inflammation around the attachment and erodible elements was slightly greater in degree and in physical extent around devices implanted in the tongue, as compared to those implanted in the palate. This is presumably due to the increased tissue mobility in the tongue, as compared to the palate, which results in stimulation of a more prominent fibrous and inflammatory response and variable dilation of the fibrous encapsulation that forms around the implanted devices. Healing was excellent at 12 months indicating a stable tissue response between 6 and 12 months with no progression of fibrosis and decreased inflammation suggesting a high degree of biocompatibility.

There are complexities that are often encountered in modeling tissue. One is that tissue is non-linear and it does not react in one to one correspondence of force and motion. [8,9,10] Secondly, while excised tissue from many sources has been well characterized, obtaining precise physical parameters for in-vivo tissue is more difficult and is an active area of research. [11,12] Thirdly, there is the unavoidable variability from individual to individual. Despite these complexities a

thorough understanding of how to apply FEA to tissue is available and has been applied to describe the reaction of the tongue to the effect of implants.

Several other modifications of the implant evaluated increases in modulus or diameter of the implant, double implants and looped implants. In these cases the strength of contraction was greater compared to the model which represented the 2 mm diameter 4830 material. As a result the motion of the tongue was less, but the relative results were the same. In all cases, there is a significant reduction in the distance the base of the tongue displaces toward the pharyngeal wall.

Distance from the base of the tongue has a profound effect on the posterior motion. The horizontal position appears slightly less effective than the lower insertion which is positively affected by its proximity to the jaw and as a consequence should be more effective. This positive effect is most pronounced in the longest implant investigated. However, in the lower position the implant may have a tendency to bend toward the base resulting in a decrease in effectiveness. The greater effect is produced by placing the implant distal end near the base of the tongue.

In all cases, there is a significant reduction in the distance the base of the tongue displaces toward the pharyngeal wall. The effects produced show resistance to tongue displacement due to gravity and negative pressure. This displacement is not expected to significantly limit motion during normal swallowing and speech function as defined in the cited references.

CONCLUSIONS

Biocompatible implant data from canines demonstrates a favorable safety profile allowing for future human clinical trials. FEA analysis demonstrates Implant properties consistent with the support of human tongue and palate structures during sleep. The model predicts that the implant

will limit tongue motion under the force of gravity and pressure while not significantly limiting motion during normal swallowing and speech function. It also suggests that altering position, material properties or design of the implant will result in predictable changes in tongue relapse.

This minimally invasive approach to targeting both the palate and base of tongue, the two levels of potential obstruction in patients with OSA, may provide a therapeutic option for OSA. This therapy is not dependent on the patient's ability to be adherent, thus providing continuous respite from upper airway obstruction.

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Figure 1

Figure 2

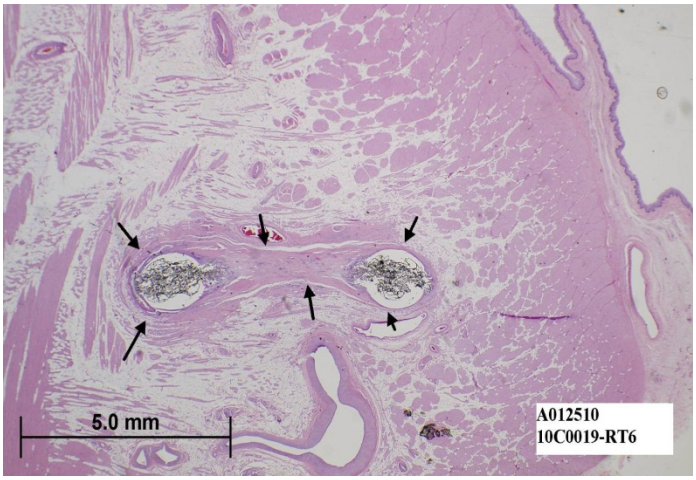

Figure 3

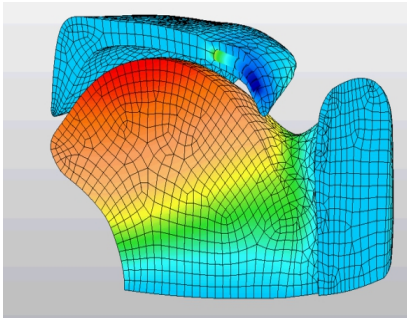

Figure 4

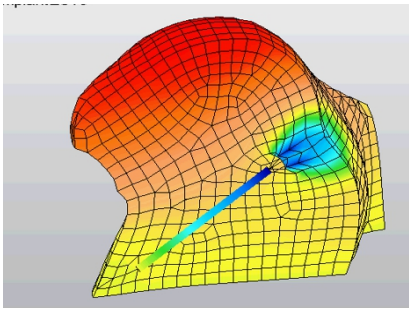

Figure 5

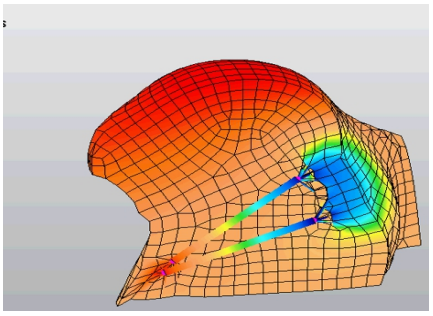

TABLE I: Tissue Response Inflammation Scores

Inflammation Grade	Palate Implants		Tongue Implants	
	6 mo.	12 mo.	6 mo.	12 mo.
Grade 0: None	0	6	0	4
Grade 1: Minimal	19	4	11	6
Grade 2: Mild	4	2	4	2
Grade 3: Moderate	1	0	2	0
Grade 4: Abscess	0	0	1	0
Mean Score All Elements	1.25 ± 0.53	0.67 ± 0.77	1.61 ± 0.92	0.83 ± 0.72
Mean Score Erodible Elements	1.37 ± 0.52	0.63 ± 0.74	1.50 ± 0.84	0.25 ± 0.50
Mean Score Attachment Elements	1.18 ± 0.54	0.75 ± 0.96	1.67 ± 0.98	1.14 ± 0.69

Figure Captions

Figure 1: ReVENT Medical Implant. A PLG bioabsorbable polymer is coiled around the silicone elastomer element with platinum/iridium markers and non-woven polyester attachment elements on either end.

Figure 2: Tongue, attachment element, animal 10C0019, right, H&E. Minimal inflammatory response around device. This represents typical appearance of minimal, Grade 1, inflammation. Note localized reaction limited to area immediately surrounding attachment element (demarcated by black arrows). There is no significant extension of fibrosis or inflammation beyond immediate implant site into the adjacent tongue, which is microscopically normal.

Figure 3: An FEA model of the palate implant

Figure 4: An FEA model of the single implant

Figure 5: An FEA model of a double implant