Protocol Title: Effect of Ultrasound Guided Laser Ablation Therapy on Symptomatic Benign Thyroid Nodules

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Study Methods

The primary objective of this study was to assess the effectiveness of percutaneous laser ablation under ultrasound guidance for the treatment of symptomatic benign thyroid nodules. The secondary objectives were to examine the safety and tolerability of this treatment technique.

The study was approved by the Mercy institutional review board and Investigational Device Exemption was obtained from the US Food and Drug Administration.

Device

The ECHOIASER X4 laser system (ElestaSpA) and its disposable kit (needle and optical fibers) have been Conformite Europeenne- marked for marketing in Europe since 2008. In addition, the ECHOIASER X4 laser system received US Food and Drug Adminis- tration 510(k) Premarket Notification approval as a substantially equivalent device on September 4, 2018. The ECHOIASER X4 sys- tem is a medical laser equipped with up to 4 diode laser sources at 1064-nm wavelength, with a maximum power of 7 W per source.

Study Population

The inclusion criteria consisted of the following: male or female aged ≥18 years, thyroid-stimulating hormone (TSH) levels within normal limits, solid thyroid nodule with <20% cystic component measuring

between 29 mm and 60 mm in the longest dimension as confirmed by ultrasound imaging, symptoms from the nodule, such as tightness or pressure in the neck, neck tenderness, neck pain, difficulty swallowing, voice changes, shortness of breath, or cosmetic disfigurement, nodule confirmed as cytologically benign by biopsy within 2 years, ability to place the laser tip inside the nodule while keeping vital structures outside the zone of injury, with a minimum distance of 17 mm anterior to the vital structures and 10 mm in all other dimensions based on the planning software, not on anticoagulants or the ability to stop anticoagulants for an appropriate period based on the pharmacology of the drug, and able and willing to provide informed consent.

The exclusion criteria for the study were as follows: pregnancy, hyperthyroidism, malignant thyroid nodule, egg-shell or coarse calcification in the thyroid nodule on ultrasound imaging, being on anticoagulation that cannot be stopped because of medical reasons, coagulopathy, a thyroid nodule in contact with the trachea, esophagus, or major blood vessels on ultrasound imaging, prior neck surgery, prior radiation to the head and neck, previous radioactive iodine treatment, current iodine supplementation, current antithyroid medication, biotin supplementation within 2 days before enrollment, allergy or contraindication to use of ChloraPrep and/or Betadine products and/or product ingredients, allergy to ethyl chloride spray or lidocaine, physical or psycholog- ical conditions preventing safe administration of the procedure, and individuals who cannot read and understand English. Written informed consent was obtained from all patients.

Study Design and Intervention

This was a single-center, prospective, nonrandomized, open- label, interventional pilot study.

Baseline assessments included history and physical examinations, visual inspection of the neck at 1 m, symptom, and cosmetic disfigurement survey (TSH, Free 14, Free 13, and antithyroid anti- bodies were obtained if not completed within 3 months before enrollment) and an ultrasound of neck with Doppler. A biopsy with fine needle aspiration was performed if a biopsy had not been performed within 2 years of enrollment and/or if a benign nodule had grown >30% in the last 2 years or there was development of new suspicious sonographic features.

All enrolled subjects underwent pre-procedure direct laryngoscopy performed by otolaryngology to assess vocal fold mobility and establish the baseline status of vocal fold structure and function.

At the study treatment visit, history and physical examinations, visual inspection of thyroid/neck at 1 m, symptom and cosmetic disfigurement surveys, qualitative β-human chorionic gonadotropin for women of childbearing potential, prothrombin time/ international normalised ratio for patients on anticoagulants, and ultrasound of thyroid/neck with Doppler were performed.

Anticoagulation medications were stopped 48 hours before the laser ablation procedure and antiplatelet medications were stopped 72 hours before the laser ablation procedures for subjects taking these medications. Subjects were permitted to take a one-time dose of a prescribed oral anxiolytic; alprazolam 0.5 mg, lorazepam 0.5 mg, or clonazepam 0.5 mg for acute procedural anxiety one hour before the procedure if indicated by the study investigator (J.T.) after discussion with the subject.

Laser precautions were followed. The procedure was performed using a sterile technique under sterile conditions.

The planning of the laser ablation procedure, insertion of needles, and monitoring of the procedure were carried out with ultrasound guidance. The Echolaser Smart Interface (ESI, Elesta SpA) facilitated the insertion of the needles and the positioning of the needles into the target lesion. The laser energy

was transmitted from the laser energy source via bare-tip optical fibers (flat-tipped quartz optical fibers with a diameter of 300 µm, Oberon GmbH). The fiber was inserted into the thyroid nodule using a 21-gauge needle introducer. Guidance was provided by the ESI and verified using ultrasound. The ESI guiding systems have been designed to help the operator position several fibers inside the lesion to be treated. The software displays the guidelines on the screen for each different guide and angle for evaluation of the best positioning of the applicator in reference to the size, morphology, and position of the lesion. After the introducer needles have been positioned, the ESI allows for verification of the needle position using the effective needle position recalculating the estimated thermal treatment area. ESI estimates the zone of injury to avoid damage to vital structures.

The fiber and needle are the only system components that come into contact with the patient and they come prepackaged as sterile disposable (single-use) kits. The optical fiber and needle are provided in ethylene oxide sterilized packaging. The total energy to be applied was calculated based on the manufacturer's guidelines. After completion of laser ablation, the fibers were removed followed by extraction of the needle(s), and hemostasis was achieved by application of pressure at the site. External bleeding was assessed by visual inspection following extraction of the needle. Internal bleeding and potential nodule rupture were assessed by ultrasound of the neck with Doppler flow performed by the investigator.

Baseline vital signs were obtained before the start of the procedure. Subjects were monitored closely during the procedure and continuous heart rate and oxygen saturation monitoring was performed. Subjects were observed in the clinic for a minimum of one hour after the procedure with procedure site inspection and examination of vital signs performed.

Subjects were asked to complete a pain assessment before the procedure and a pain assessment and tolerability assessment before discharge from the clinic. Subjects were contacted by telephone within 2 days after the study procedure for follow-up and assessment of adverse events.

Follow-up visits were performed at 3, 6, and 12 months after completion of the study procedure. History and physical examinations, visual inspection of thyroid/neck at 1 m, and ultrasound of thyroid/neck with Doppler were performed at all visits. A pain assessment was performed at 3 months and the symptom and cosmetic disfigurement surveys were performed at all visits. TSH and Free T 4 were obtained at 3 and 6 months and TSH, Free T 4, and antithyroid antibodies were collected at the 12th month of follow-up visit. Adverse events were monitored throughout the study. Physical examinations, visual inspection of neck region at 1 m, ultrasound with Doppler examinations, and the laser ablation procedure were performed by the same investigator for all subjects.

Data Collection and Statistical Analysis

Visual inspection of the neck region was performed at a distance of 1 m from the subject. The presence or absence of a cervical lesion was documented using the following scale: 1 - nodule not visible; 2 - nodule visible only with hyperextended neck; and 3 – nodule visible at a distance > 1 m. All ultrasound examinations of the neck with Doppler were performed using the GE Logiq P6 ultrasound. The nodule volume (in ml) was calculated using the following equation: volume = length (cm) x width (cm) x depth (cm) x 0.52[i]. The nodule volume percent was calculated using the following equation: volume reduction percentage = (1 - final volume/initial volume) x 100.[ii] Results of laboratory assessments obtained as described above were collected. For pain assessment, subjects were asked to rate their neck pain on a scale from 0 to 10, where 0 indicated no pain and 10 indicated worst pain possible. Subjects that reported neck pain were asked to indicate the location of the pain. Local symptoms were evaluated with a questionnaire adapted from the questionnaire used in the study

conducted by Papini et al.[iii] The questionnaire assesses the presence or the absence of the following symptoms: neck constriction, cervical tenderness, dysphagia, dyspnea, and dysphonia. In addition, subjects were asked whether the thyroid nodule is causing cosmetic disfigurement to assess the cosmetic impact of their thyroid nodule on a scale from 0 to 10 where 0 indicated not at all and 10 indicated very much. Tolerability assessment was performed after the procedure using a questionnaire consisting of the following 3 questions with Likert scale responses: How likely is it that you would have the laser ablation procedure again? How satisfied were you with the length of the laser ablation procedure? How much discomfort did you have with the laser ablation procedure? The pain, symptoms, and cosmetic and tolerability assessments were performed for subjects.

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[i] Seo SH, Kim TH, Kim SH, et al. Predicting the size of benign thyroid nodules and analysis of associated factors that affect nodule size. Chonnam Med]. 2015;51(2):97-101.

[ii] American Thyroid Association. Change in thyroid nodule volume calculator. Accessed June 21, 2023. https:J/www.thyroid.org/professionals/calculators/ thyroid-with-nodules/

[iii] Papini E, Rago T, Gambelunghe G, et al. Long-term efficacy of ultrasound-guided laser ablation for benign solid thyroid nodules. Results of a three-year multicenter prospective randomized trial.] Clin Endocrinol Metab. 2014;99(10): 3653-3659.