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In vivo Results for Interstitial Laser Application in Thyroid Gland

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Abstract
Objective: Aim of this study was to evaluate the potential of denaturation of hormone active tissue in the thyroid gland by laser induced interstitial thermotherapy (LITT) as a treatment of autonomous hyperthyroidism.
Materials and Methods: An interstitial thyroid laser application (Nd:YAG 1064nm, 5W, 2min) was performed in 5 pigs. During laser application, the laryngeal recurrent nerve was controlled electro-physiologically. Postoperatively, TSH, total T_3 (TT_3) and free T_4 (FT_4) were measured regularly. After a follow-up period of up to 6 weeks, pigs were sacrificed and the thyroid glands were evaluated histological.
Results: A malfunction of the nerve due to laser treatment was not detected. During the first postoperative week there was a decrease of both FT_4 and TSH whereas TT_3 showed an extreme decline of its plasma levels reaching nearly the detection limit. All values showed a recovery to their initial levels during an interval of 10 days and than increased to levels sometimes higher than baseline. The coagulation zones were demarcated clearly towards normal tissue with increasing fibrosis of the treated areas.
Conclusion: Interstitial thyroid ablation using a Nd:YAG laser is a minimal invasive, safe and effective procedure. Further evaluation including long term follow-up in humans is needed to confirm these results.

Key words: interstitial laser therapy, thyroid gland, Nd:YAG laser

Abbreviations: LITT = laser induced interstitial thermotherapy, FT_4 = free tyroxine, TT_3 = total triiodothyronine, Nd:YAG = Neodym Yttrium Aluminium Granat, US = ultrasound

Introduction

Hyperthyroidism is a severe illness traditionally treated with anti-thyroid drugs, radioiodine therapy and surgical subtotal resection. Usually in most patients the medical treatment with anti-thyroid drugs achieves a normal thyroid function. Potential side effects like allergic reaction, dysgeusia, and in some cases agranulocytosis are described. A long term medical therapy is justified only in patients who are not allowed to receive radioiodine therapy or surgical intervention. A disadvantage of radioiodine therapy is isolation of patients for several days due to radiation protection and safety precautions regarding hazardous radioactive materials. In addition, post-radiation hypothyroidism is described in 25% of all patients as a long term side effect [23].

The surgical resection of the thyroid and parathyroid gland requires general anesthesia. There is a potential risk of intra-operative injury of the laryngeal recurrent nerve as well as laceration of the parathyroid gland resulting in postoperative hypocalcemia [8]. Although minimally invasive methods can be performed for thyroid and parathyroid surgery, there is still a demand for specific non-surgical procedures especially for the group of high risk patients. This lead to ultrasound (US) guided percutaneous ethanol injection resulting in colliquative necrosis in areas where ethanol was injected. [1, 10, 11, 19]. Unfortunately, ethanol injection does not ablate tissue with regular, homogeneous and reproducible pattern in a single application. On the other hand, the technique of US guided laser induced interstitial thermotherapy (LITT) has become useful in tumor palliation for patients with different kind of advanced stages of cancers. [3, 12].

The thermal effect is a fundamental property of laser radiation in biological tissue. Coagulative and hyperthermic effects due to photon absorption and heat conduction lead to an immediate or delayed tissue destruction. [15, 16, 19, 21]. LITT is a minimally invasive technique of focal tissue ablation and has also been introduced for ablation of benign tumors. [4, 13, 14].

The aim of this study was to achieve a histological and endocrinological effect with a single minimal invasive procedure. Furthermore, another aim of this study was to evaluate the risk of laser induced thermal volume reduction of the thyroid gland.

Material and Methods

The Laser Application-System

We used a Nd:YAG-Laser (1 064 nm), continuous power (5 Watt over 2 minutes).

The light was applied interstitially with a bare fiber (0.6 mm)

Animals and Treatment

Interstitial laser coagulation was tested in thyroid glands of 5 pigs. (the animal experiment was approved by the local representative government authority at Tübingen; file number 35/9185.81-3).

All animals were operated in general anesthesia. We performed a sagittal incision of the neck for preparing the left as well as the right thyroid lobe. At the same time the laryngeal recurrent nerve was prepared and demonstrated. After this procedure the nerve was punctured with electrodes caudal and cranial. The nerve was stimulated electrically using this electrodes with single rectangle impulses (200 µV, 20 mA electrical stimulation with a duration of 0,1 ms). The consecutive response of the nerve was measured in a distance of 5 cm from the stimulated point and was documented continuously during the laser experiment.

For LITT the thyroid gland was punctured with a 1 mm thick cannula. After removal of the mandrin guide the fiber (0.6 mm) was inserted until it reached the end of the cannula. The needle was withdrawn leaving the fiber tip in direct contact with the tissue (Fig. 1). During the laser procedure, pulse, blood pressure, body temperature and the respiratory rate of the animals were measured continuously. After 2 minutes the fiber was removed and the puncture channel was closed with one suture. In one animal a laser accident was simulated. Therefore a direct laser application on the laryngeal recurrent nerve was performed additionally. This animal was sacrificed after the procedure with an overdose of narcotic drugs and the thyroid gland was removed.

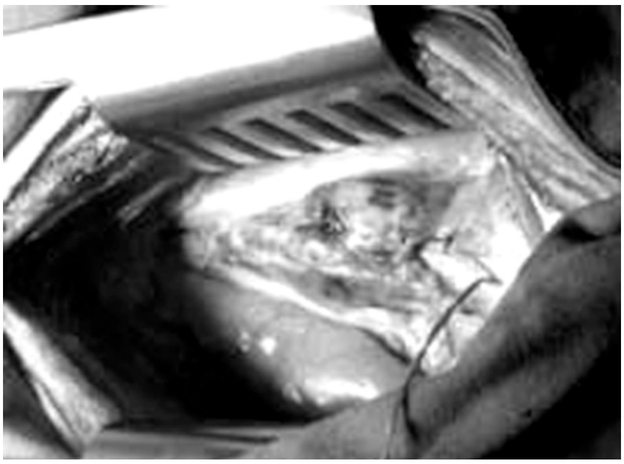

Fig. 1. Thyroid gland with an edematous effect after interstitial laser application. A temperature probe is placed near the laryngeal nerve.

The other four pigs survived 1, 2, 4 and 6 weeks after the laser treatment. After that time they were sacrificed. Blood samples of these animals were regularly drawn before and after the procedure for investigating the hormone effect. The blood was drawn in the first two weeks 2 times a week and then only once a week. We investigated TSH, free T_4 (FT_4) and Total-T_3 (TT_3) plasma levels. After the animals were sacrificed the thyroid gland was removed totally and a histological examination was performed.

Results

The placement of the laser fiber by puncturing the thyroid gland could be done without loss of blood. Bleeding during and after the procedure was avoided by drawing the applicator slowly back coagulating the channel of puncture. The animals showed no systemic reaction during the laser procedure. The surface of the thyroid gland was macroscopically inconspicuous during and after the laser application. In one case the coagulation was performed close below the surface of the thyroid gland. This area showed a livid coloring of the capsule. The coagulation zones felt hard and the effected areas were easy to differentiate against normal tissue. Macroscopically the fresh coagulation zones in the terminal animal showed a central channel of puncture with small areas of carbonization and peripheral mild pink coagulated tissue, clearly demarcated from normal parenchyma. This zone was surrounded by an interstitial edema. The coagulation zones showed diameters of 5 to 8 mm [17].

At 4-6 hours after anesthesia all animals showed normal eating and movement behavior and were found clinically healthy in further controls. No complication, such as bleedings, dyspnea or secondary sepsis, were registered until the end of the experiment.

One week after laser application we found a border of granulation tissue around the coagulation zone, which was increased in thickness and became more fibrotic from week to week. Four weeks after laser procedure we found only small remnants of the former coagulation zone. Bacteriological and cytological tests showed sterile necrotic tissue.

Neurophysiology

The function of the laryngeal recurrent nerve was not affected by the laser procedure in all animals. The electrical nerve response at the beginning and after the laser procedure was similar in all stimulation tests (Fig. 2).

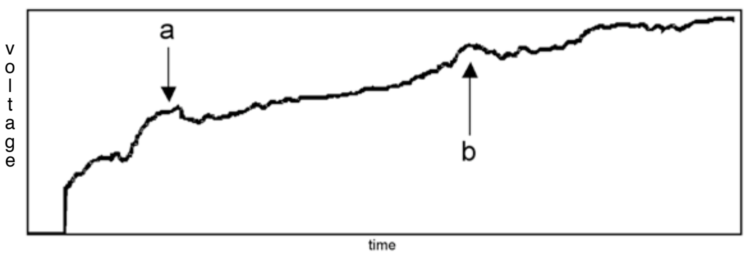

Fig. 2. Electrical stimulation of the laryngeal recurrent nerve (a: single rectangular impulse, 200 µV, 20 mA, 0,1 ms) with following nerve responses (b: distance 5 cm from electrical stimulus, Delay 1,75 msec, Amplitude 180 µV.

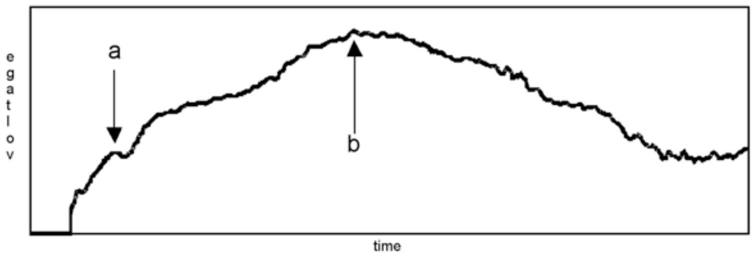

Fig. 3. Identical electrical stimulation of the laryngeal recurrent nerve like in Fig. 2 (a) with weak nerval response (b) after direct light exposition.

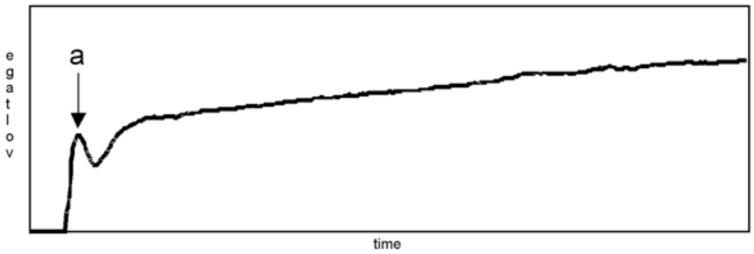

Fig. 4. Identical electrical stimulation of the laryngeal recurrent nerve like in Fig. 2 after direct laser irradiation of the nerve. The action potential of the nerve has disappeared.

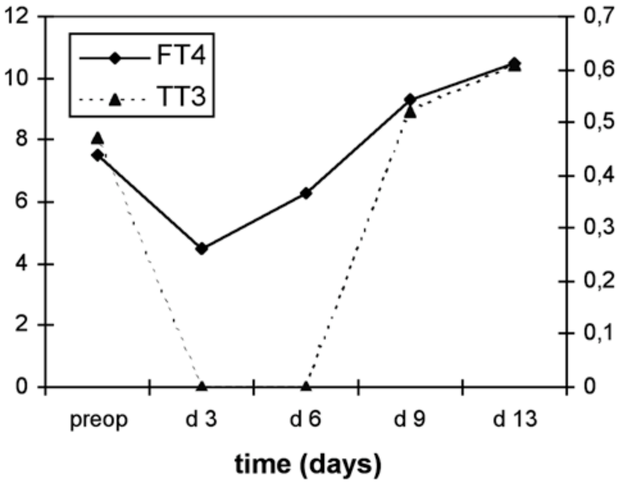

Fig. 5. Preoperative and postoperative TT_3 and FT_4 Levels of a pig (2 weeks survival time after LITT)

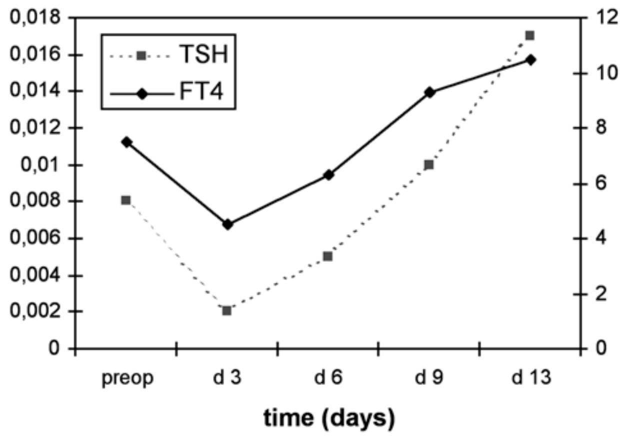

Fig.6. Preoperative and postoperative TSH and FT_4 levels of a pig (2 weeks survival time after LITT)

In the simulated laser accident the laser beam was directed to the laryngeal recurrent nerve. Initially we observed normal nerve responses but increasing tissue temperature showed weaker nerve response until the nerve lost its function. (Fig. 3 and 4).

Because of the low laser power (5 Watt) this effect appeared only after a time period longer than 1 min. Obviously the optical properties of the nerve tissue with its fat like appearance is similar to that of fat tissue with small light absorption.

Endocrinology

After LITT TSH first showed a decline, which was different in all animals. After one week there was a recovery of the TSH-decline with excess values. FT_4 showed a similar approach like TSH with a short-time decrease of plasma levels for one week followed by increasing values in 3 animals also elevated to even higher than baseline values.

In all animals TT_3 reacted in a significant way. It declined in all animals in a very short period of time (3-6 days). Also in this case values were dropping below the detection values (< 0.4 µg / l).

Discussion

Absorption of photons in biological tissue leads to a local increase of the temperature. 60°C is considered as a irreversible destruction of proteins. Amount and volume of local temperature rise depends on several parameters like power density, wavelength and the optical tissue properties. Further spreading of the coagulation zone results from local heat conduction. The critical zone for laser light application is the fiber tip as a result of the very high local power density. Carbonization of the coagulation zone further promotes the heating up to vaporization, because the optical properties of carbonized tissue layers increases absorption more and more. This causes charring and limits the further growth of the coagulation zone by direct laser heating.

Experimental studies in the past have shown big homogenous coagulation zones in other organs with different application systems [16, 19, 21]. However, adenomas of thyroid- or parathyroid gland are small.

Therefore the best application form seemed to be a bare fiber with low power output inserted in the center of the adenoma. With these modalities, coagulations volumes of 1 cm^3 can be achieved which is sufficient for most indications.

In our study, LITT appeared feasible and handling was easy. US can be used to target thyroid lesions, guiding interstitial optical fiber insertion according to the procedure described for percutaneous ethanol injections [3-5]. Small optical fibers allow the use of fine needles, which prevent local discomfort. In a feasibility study, Pacella et al. [19] reported on only mild burning sensation during laser firing, compared to the minimal painful procedure of fine-needle aspiration biopsy. No tissue damage was induced at the skin or at the needle duct.

US monitoring during laser irradiation depicts as a irregular hyperechoic area enlarging over time and is more secure than the uncontrolled alcohol application [6, 23]. However, exact prediction of the extent of the coagulation zone is difficult due to microbubbles and reversible edematous borders. In previous studies real-time imaging of the coagulation zone served only as a rough guide to the extent of necrosis [15, 18].

Magnetic resonance imaging guidance is reported to provide clear and accurate monitoring of temperature and laser-induced tissue damage in the treated area in experimental models and in clinical studies. However, this technique is time-consuming and expensive [22]. In our animal model, a time interval of 2 minutes for laser application was sufficient enough to reach coagulation zones between 5 to 8 mm in diameter. Coagulation zones larger than 8 mm in small thyroid glands of young laboratory pigs are not desirable.

The endocrinological coagulation effect was established immediately, since low levels of FT_4 were achieved within a week. After this, FT_4 levels were reaching baseline values and in some cases even exceeding these levels. This phenomena can be explained by the young laboratory animals with a strong growth rate and endocrinological recompensation. This could also explain the strong decline of the biological more active T_3, which is synthesized from T_4, falling shortly under the detection limit. So far, the decline of TSH after the procedure remains unclear. May be, other factors like release of cell components, hormone metabolites and iodine lead to the short-time decline of TSH, but later on to a overcompensation higher than the baseline values.

On the other hand, the thyroid gland has a capacity to reduce thyroid hormone production in the presence of excessive iodine by reducing the organification of the iodine. This Wolff-Chaikoff effect is observed after 48 hours and protects the organism from excessive synthesis of the thyroid hormones. This effect is usually temporary and within a few days thyroid hormone synthesis returns to normal level through the so called 'escape' phenomenon. However, in few normal individuals and in some susceptible patients, the escape does not occur [21]. The histological examination of the coagulation zone showed nearly a complete conversion to fibrotic tissue during a time interval of 4 weeks. Irregular pattern of tissue damage, characteristic for percutaneous ethanol injection, due to the uneven distribution of ethanol within the tissue were not found after LITT. In our animal model the different coagulation diameters were a result of a variance in the applied energy and the local blood perfusion. The cooling effect of larger vessels in the area was described in liver coagulation by others [16, 19, 21]. This physical phenomenon could reduce the effectiveness of LITT in a significant and unpredictably way in the surrounding of cystic tumors.

The cooling effect of larger vessels is also a protection against occlusion and thermial damage. This may also be an effect helping to protect the ramus recurrent of the laryngeal nerve, which has a physiological course between the thyroid gland and the large cervical perivascular sheath in a regular anatomy. This may contribute to the protection of the larynx recurrent nerve since laser therapy did not result in any nerve irritation or damage.

Furthermore, the white nerve tissue similar to fat tissue shows only weak light absorption. Also the heat conduction of nerve tissue might be smaller compared to thyroid tissue, resulting in heat protection when applying LITT [5, 7]. Also the slow decrease of the nerve response due to direct laser irradiation (~ 1 min) potentiates the opportunity for a clinical function test so that a accidental nerve lesion can be avoided during laser therapy. US guided percutaneous LITT has been proven to be useful for palliation of malignant as well as benign tumors, and has recently been evaluated in a study of recurrent thyroid carcinoma [18]. Unlike interstitial ethanol injection, laser induced tissue damage can be effected in a controlled and safe fashion, causing no damage to the surrounding tissue [2, 6, 23]. Histological examination of tissue after LITT confirms the presence of a well defined necrotic area, demonstrating the ability of this technique to cause controlled thermal necrosis [9, 22].

In our animal experiment, LITT was well tolerated without any side effects or complications. Although LITT application in the thyroid gland had undergone tissue reduction, the question of long-term efficacy remains open in the case of nodules/tumor treatment. Repeated treatment could be considered in the case of relapse. These preliminary results suggest that US guided LITT is a feasible, minimally invasive technique for focal thyroid nodules/tumor ablation and may be a useful non-surgical alternative for selected patients for whom surgery is contraindicated. Long term human studies should follow to answer this question.

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