RAPID COMMUNICATION

A randomized controlled trial to evaluate the efficacy of ultrasound-guided laser photocoagulation for treatment of benign thyroid nodules

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ABSTRACT. This randomized controlled study was designed to test the efficacy and safety of percutaneous ultrasound (US)-guided laser photocoagulation (PLP) for treatment of subjects with compressive symptoms due to benign thyroid nodules and/or at high surgical risk. Twenty six subjects were randomized to the intervention (no. 13, age 68±3 yr, mean±SEM) or observation (no. 13, age 71±2 yr) groups. In the control group, the volume of nodules did not significantly change over the 30 week period of observation. In the intervention group, median nodule volume at baseline was 8.2 ml (range 2.8-26.9) and was not significantly different from that of the control group. Nodules decreased significantly ($p<0.0001$) by 22% after 2 weeks (6.5ml; range 2.4-16.7) and by 44% after 30 weeks (4.6 ml; range 0.69-14.2). Energy given was correlated ($p<0.05$) with the reduction of thyroid nodule volume. All patients tolerated the treatment well and reported relief from compressive and cosmetic complaints ($p<0.05$). At the time of enrolment 7/13 (54%) and 6/13 (46%) of patients in the intervention and control groups, respectively, had sub clinical hyperthyroidism. PLP normalized thyroid function at 6 and 30 weeks after treatment. In conclusion, PLP is a promising safe and effective procedure for treatment of benign thyroid nodules in patients at high surgical risk.

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INTRODUCTION

Surgery is the standard therapy for benign thyroid nodules causing symptoms of compression. Alternative treatments have been proposed to reduce the size of benign nodules of patients with old age and/or high surgical risk. Percutaneous ethanol injection appears to be effective for treatment of mixed nodules but does not show an encouraging benefit/risk profile for treatment of solid thyroid nodules (1). In these cases, percutaneous ultrasound (US)-guided laser photocoagulation (PLP) appears to be a promising therapeutic approach (2-8). PLP is a minimally invasive procedure, proposed for treatment of thyroid nodules by Pacella et al. (3, 4, 8) and, subsequently, by Spiezia et al. (5) and Dossing et al. (6, 7), that has been successfully used to ablate benign and malignant tumors (2-8).

We report the results of a randomized controlled study designed to evaluate the efficacy and safety of PLP in subjects with a multinodular goiter or single benign nodules causing compressive symptoms. The patients included in the study were not candidates to thyroidectomy because of high surgical risk or refusal to intervention.

SUBJECTS AND METHODS

Twenty six subjects with compressive symptoms due to multinodular goiter and at high surgical risk were randomly assigned to one session PLP treatment (no. 13) or observation (no. 13). The study was approved by local Ethical Committee and written informed consent was obtained from all subjects. The sample size of the study (13 patients/group) was based on the results of previous studies (2-8),

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in order to achieve 81% power with a reduction in nodule size of 35% in the intervention group (2-8), group SD of 30% and a significance level (α) of 0.05, using a two-sided two sample t-test.

Diagnosis of benign nodules was obtained through fine needle aspiration biopsy (FNA). FNA was performed in all nodules with a volume >1 ml. The clinical features of the patients randomized to the intervention and control groups are reported in Table 1. Median age of the intervention group was 63 yr (52-92 yr), that of the control group 70 yr (62-81 yr). At the time of enrolment, 7/13 (54%) and 6/13 (46%) of patients in the intervention and control groups, respectively, had subclinical hyperthyroidism. Thyroid scan was performed in all patients affected by subclinical hyperthyroidism. Thyroid scan demonstrated cold or mild hyper-functioning nodules, no patient had a single hot nodule.

PLP was performed under sterile conditions and US guidance as described by Pacella et al. (8), with the exception that a single 21-gauge spinal needle was used. The needle under US guidance (US scanner Technos MPX, Esaote, Genova, Italy) was positioned in the center of the dominant thyroid nodule, at about 1 cm of distance from the caudal portion of the capsule. Subsequently, a laser 300-μ quartz fiber was inserted in the lumen of the needle, leaving 5 mm of the fiber out of the needle, and patients were

Table 1 - *Sex, age (yr), US nodule appearance [mixed (M), solid (S)], energy given [Joule (J)], volume size (ml) at baseline, 2, and 30 weeks after treatment or inclusion in the study; thyroid function [normal values: free T_3 (FT_3) 2.3-4.2 pg/ml, free T_4 (FT_4) 0.8-1.76 ng/ml, and TSH 0.35-5.5 μUI/ml] before, 3 days and 6 weeks after treatment or inclusion in the study of subjects randomized to intervention or control (energy 0) groups.*

Sex	Age	Nodule	Goiter or single nodule	Joule	Vol. basal	Vol. 2 weeks	Vol. 30 weeks	FT_3/FT_4/ TSH before	FT_3/FT_4/ TSH at 3 days	FT_3/FT_4/ TSH at 6 weeks
F	74	M	Goiter	1800	6.13	7.15	4.3	3.8/1.6/ 0.28	4.8/1.8/ 0.18	3.4/1.3/ 0.7
F	59	S	Goiter	2100	12.4	7.7	4.6	3.9/1.7/ 0.22	5.5/1.9/ 0.10	3.5/1.4/ 0.5
F	66	M	Goiter	2100	8.17	5.93	5.9	3.4/1.5/ 0.30	4.5/1.7/ 0.22	3.0/1.2/1.4
F	63	S	Single	1800	26.94	12.49	12.6	3.0/1.2/ 2.30	3.5/1.3/ 2.22	3.0/1.3/ 2.34
F	52	M	Goiter	2200	7.22	4.43	0.69	3.4/1.5/ 0.15	4.9/1.9/ 0.08	3.6/1.7/ 0.92
F	81	S	Single	1900	16.13	15.11	11.2	3.1/1.4/ 0.33	5.2/2.0/00.28	3.3/1.3/ 1.82
F	62	S	Goiter	1500	2.84	2.4	1.26	2.6/0.9/ 1.33	3.2/1.3/ 0.98	3.0/1.2/ 1.52
F	56	M	Goiter	1200	5.27	5.6	5	2.8/1.2/ 0.63	4.4/1.5/ 0.29	2.9/1.5/ 1.44
F	64	M	Goiter	1400	5.32	3.6	2.1	3.8/1.6/ 0.09	6.4/2.3/ 0.06	3.9/1.6/ 0.74
F	92	M	Goiter	1600	8.58	4.29	3.9	2.4/1.1/ 1.29	4.5/1.8/ 0.26	2.9/1.2/ 1.74
F	61	S	Single	2100	20.5	16.7	14.2	2.9/1.4/ 0.29	3.5/1.8/ 0.24	2.6/1.4/ 1.24
M	63	S	Goiter	1600	8.4	7.6	3.8	4.0/1.4/ 2.29	3.7/1.6/ 2.24	3.5/1.4/ 2.35
M	84	S	Goiter	700	6.9	6.5	4.9	3.0/1.3/ 2.44	3.3/1.4/ 2.26	3.7/1.2/ 2.47
F	66	M	Goiter	0	8.1	8.10	8.7	3.8/1.5/ 0.14	3.9/1.6/ 0.26	3.7/1.6/ 0.27
F	80	S	Goiter	0	9	8.90	8.8	3.5/1.3/ 1.44	3.6/1.5/ 1.60	3.8/1.5/ 1.77
M	77	S	Goiter	0	11	11.20	11.1	2.7/1.2/ 1.84	2.6/1.3/ 1.93	2.8/1.4/ 2.66
M	62	S	Goiter	0	7	7.30	7	2.5/1.3/ 1.55	2.4/1.4/ 1.23	2.9/1.3/ 1.46
M	70	S	Goiter	0	7.8	7.90	7.6	3.5/1.6/ 0.21	3.4/1.7/ 0.23	3.9/1.5/ 0.26
F	62	M	Single	0	12	11.60	11.4	3.8/1.4/ 0.11	4.0/1.7/ 0.14	4.1/1.5/ 0.14
F	63	S	Goiter	0	9.2	9.20	9.2	3.1/1.1/ 1.71	3.0/0.8/ 1.83	3.1/1.0/ 2.10
F	69	M	Goiter	0	7.3	7.10	7.3	3.4/1.4/ 1.21	3.2/1.2/ 1.13	3.3/1.3/ 1.15
F	71	S	Goiter	0	7.2	7.20	7.3	3.6/1.6/ 0.11	3.8/1.6/ 0.10	3.8/1.7/ 0.05
F	69	M	Goiter	0	7.1	7.00	7.3	3.8/1.5/ 0.21	3.6/1.6/ 0.13	3.5/1.5/ 0.15
F	81	M	Goiter	0	8.1	8.50	8.7	2.9/1.1/ 1.22	3.6/1.6/ 0.13	3.5/1.5/ 0.15
F	80	S	Goiter	0	8.2	8.00	8.2	4.1/1.5/ 0.08	4.1/1.6/ 0.10	3.9/1.5/ 0.09
F	71	S	Goiter	0	7.7	7.70	7.9	3.5/1.4/ 0.31	3.5/1.2/ 0.33	3.4/1.4/ 0.35

treated *via* a 1064 nm continuous-wave neodymium yttrium-aluminum-garnet laser (Smart 1064, DEKA, Calenzano, Florence, Italy). We used a continuous output power of 3 W for variable time until the interstitial hyperechoic area produced by thermal ablation reached the periphery. During the procedure the needle was moved up from the initial position by 2-5 mm to reach step by step a distance of 1 cm from the cranial portion of the capsule. At each step a variable energy of 100-400 Joule (J) was given on the basis of the extent of the hyperechoic area produced by photocoagulation. In case of wide nodules, the procedure was repeated re-positioning a further 21 gauge needle in an area of the nodule, about 1 cm further from that previously damaged. Energy administration was temporarily stopped when patients reported pain or burning symptoms. Only the dominant nodule was treated in case of multinodular goiters.

After PLP, patients were asked whether they would repeat the treatment again, as a marker of tolerability. The volume of the nodules was measured by the same investigator, blinded for treatment, using the ellipsoid formula (9), before, 2, and 30 weeks after the treatment or the inclusion in the study as controls. TSH levels, free T_3 (FT_3)and free T_4 (FT_4) were obtained at baseline, 3 days, 6 and 30 weeks after treatment. On these occasions all subjects were asked to rate a simple visual scale (1-6 cm) reporting compressive and cosmetic complaints.

FT_3, FT_4 and TSH were determined using a commercial kit of Bayers Diagnostics (Bayer Healthcare Diagnostic Division, NY, USA) with normal values of FT_3 2.3-4.2 pg/ml, FT_4 0.8-1.76 ng/ml, and TSH 0.35-5.5 µUI/ml.

Changes in the size of nodules' volumes over the 30 week period were analyzed using repeated measures analysis of covariance (ANCOVA) with treatment (laser therapy *vs* no laser therapy) as grouping factor and the baseline as covariate (10), followed by *post hoc* comparisons (Tukey's test) to pinpoint specific differences on significant interaction means. Linear regression analysis, conducted according to the least square method, was performed to look for correlation between nodule reduction and the change in laser energy delivered. Data were considered to be significantly different at $p<0.05$. The statistical packages Statistica 4.5 (Statsoft, Tulsa, OK, USA) and NCSS 2004 (Number Cruncher Statistical System, Kaysville, UT, USA) were used for analyses.

RESULTS

The results of the study are summarized in Table and Figure 1. In the control group the volume of nodules remained stable over the entire period of observation. The basal median volume was 8.1 ml (range 7-12); after 30 weeks the median volume was 8.2 ml (range 7-11,4, p=ns). The control subjects did not report amelioration of pressure symptoms.

In the intervention group, the median energy given was 1900 J (range 700-2200 J). The median nodule volume at baseline was 8.2 ml (range 2.8-26.9) and was not significantly different from that of the control group. Nodules decreased significantly ($p<0.0001$) by 22% after 2 weeks (6.5ml; range 2.4-16.7) and by 44% after 30 weeks (4.6ml; range 0.69-14.2). Energy given was correlated ($p<0.05$) with the reduction of thyroid nodule volume [volume= (-0.16) + (0.0029 x J)]. In patients with subclinical hyperthyroidism, PLP procedure was similarly effective in reducing the size of cold or mild hyperfunctioning nodules.

All patients tolerated the treatment well (5 reported mild pain or feeling of burning) and, immediately after the treatment, answered that they could repeat it. Three patients reported fever during the first twelve hours; none had pain, local infections, dysphonia or hemorrhage. A transient hyperthyroidism, demonstrated by a modest increase in FT_3 and/or FT_4 after 72 h, occurred in 8 out 13 patients. After 6 weeks, all patients of the intervention group had a normalization of FT_3, FT_4 and TSH concentrations and reported amelioration of symptoms (compressive complaints $p<0.05$; visual complaints $p<0.01$). After 30 weeks all patients of the intervention group had normal thyroid function. Thyroid autoantibodies were in the normal range in the patients of the intervention group, before and 30 weeks after PLP treatment.

DISCUSSION

The results of this randomized controlled study demonstrate that PLP is effective in reducing the volume, the compressive symptoms, and normalizing the function of benign thyroid nodules in subjects who are not candidates for surgical treatment.

In the intervention group, all patients were treated by inserting a single needle at a time and checking under US

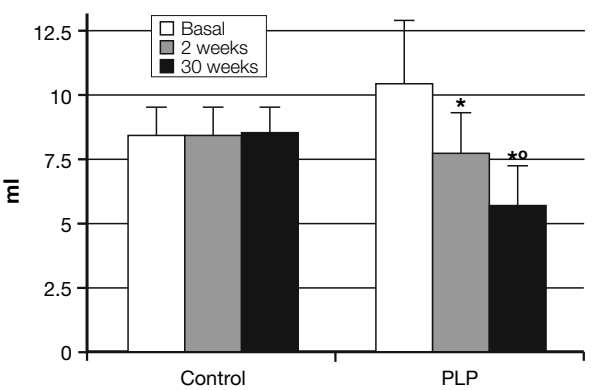

Fig. 1 - *Changes in the size (mean±SEM) of nodules before, 2 and 30 weeks after the inclusion in the study (control group) or percutaneous ultrasound (US)-guided laser photocoagulation (PLP) (*p<0.01 vs basal; °p<0.01 vs basal and control).*

guidance the extension of the damage area. The procedure was immediately repeated in case of large nodules in order to coagulate the central area of nodules, saving at least 1 cm of tissue along the periphery. Our step by step approach is more time consuming in comparison to the simultaneous insertion of more needles (3, 4, 8). However, it offers the advantage of better control, under US guidance, of the progression of the area of damage and is sufficient to reduce the size of nodules. After 30 weeks we obtained a median reduction of volume size (44 %) comparable to that reported by other groups who used more needles at the same time (3, 4, 8) or a single needle at one time (6, 7). The amount of energy given was correlated ($p<0.05$) with the reduction of thyroid nodule volume [volume = (−0.16) + (0.0029 x J)]. Accordingly, on average for every 1000 J delivery of energy (by a single needle) one should expect a decrease of about 2.7 ml in the volume size after 30 weeks.

PLP, performed as described, is a well tolerated procedure. We did not observe any side effects, with the exception of transient fever and hyperthyroidism, also reported by other authors (8), which are likely due to tissue necrosis. Interestingly, 30 weeks after treatment all patients with pre-toxic nodules had normal TSH values. This suggests that PLP, by reducing blood supply (vessel photocoagulation) and volume size (progressive necrosis), is capable of lessening the activity of hyper functioning nodules.

Regarding safety we did not observe any side effects. Other authors reported one case of transient vocal cord paralysis (5). Since the extension of the hyperchoic area does not exactly reflect the true area of coagulation, it is important to leave at least 1 cm of border between the hyperechoic area and the periphery of the nodule to prevent any damage to surrounding structures (laryngeal nerve, carotid artery, trachea) (4, 7). In addition, during the procedure we asked the patients to report if they had pain or burning symptoms. In this case, the administration of energy was temporarily stopped and the position of the needle changed by about 1 cm before re-starting the treatment. In our opinion, using this cautious approach combined with continuous US guidance, PLP is a safe procedure because it allows a close control of the energy delivered as well as of the extension of the area damaged.

In conclusion, the present randomized controlled study demonstrates that PLP is an effective procedure for treatment of a large thyroid nodule in patients with high surgical risk. Due to the reasonable costs of the equipment required (laser and US devices) and the negligible costs of consumables, it is likely that PLP will progressively increase its popularity among endocrinologists over the next few years.

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