


High intensity focused ultrasound (HIFU) ablation of benign thyroid nodule is safe and efficacious in patients who continue taking an anti-coagulation or anti-platelet agent in the treatment period

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ABSTRACT

Background: High intensity focused ultrasound (HIFU) ablation is a promising treatment for benign thyroid nodules but because bleeding complications can occur following any intervention to the thyroid gland, the safety and efficacy of HIFU ablation were evaluated in patients who continued taking an anti-coagulation or anti-platelet agent during treatment.

Methods: From 2015 to 2017, 303 patients who underwent a single-session ablation for a benign thyroid nodule were analyzed. The primary study endpoint was thyroid bleeding, intra-lesional or perithyroidal hematoma or neck bruising diagnosed within 4 days of the treatment. Other endpoints included treatment-related complications, extent of nodule shrinkage and symptom score. Nodule volume was estimated by ultrasound. Extent of nodule shrinkage (by volume reduction ratio) (VRR) = $[\text{Baseline volume} - \text{volume at 6-month}] / [\text{Baseline volume}] \times 100$. Obstructive symptom score (by 0–10 visual analog scale, VAS) was evaluated after treatment.

Results: Twelve patients continued taking an anti-coagulation or anti-platelet agent while the other 291 patients did not during treatment. No patients in either group suffered active thyroid bleeding, intralesional/pericapsular hematoma or subcutaneous neck bruising in the first 4 days of treatment. Complication rate and the 6-month VRR were comparable between the two groups (0.0% vs. 1.7%, $p = 1.000$ and 55.96% vs. 61.29%, respectively, $p = .073$).

Conclusions: HIFU ablation is a feasible treatment in patients who continue to take an anti-coagulation or anti-platelet agent during treatment and might be preferable in patients who continuously require an anti-coagulation or anti-platelet agent for one reason or another during treatment.

ARTICLE HISTORY

Received 16 August 2018
Revised 29 October 2018
Accepted 10 November 2018

KEYWORDS



High-intensity focused ultrasound ablation; thyroid nodule; anticoagulants; platelet aggregation inhibitors; hemorrhage

Introduction

Thyroid nodules are common and although most are benign and will remain relatively static over time, some do become large and cause symptoms [1–3]. Surgery has been the standard treatment in patients with a symptomatic thyroid nodule but it may result in complications, high cost and require a general anesthesia. As a result, there has been a growing interest in developing less invasive, non-surgical technique in the treatment of benign symptomatic thyroid nodules [4–6]. For predominantly-solid or solid nodules, various thermal ablation techniques including radiofrequency ablation (RFA), laser (LA) and microwave ablations have been found to be highly effective [4,5]. High intensity focused ultrasound (HIFU) is a new form of ablation technique that utilizes focused ultrasound energy to induce ablation. It has been shown to not only induce significant nodule shrinkage but also alleviate nodule-related symptoms following treatment [6–9].

However, because the thyroid gland is a vascular organ, bleeding and neck hematoma can occur following any type

of intervention involving the thyroid gland [5,10,11]. This is particularly so when the thyroid capsule has been punctured by a sharp needle or instrument such as in needle aspiration biopsy or in imaged-guided thermal ablation like RFA [11,12]. As a result, it is generally recommended based on expert opinion and consensus statement to withhold any anti-coagulation or anti-platelet agents or correct any underlying coagulopathy 5–7 days before any invasive procedure to the thyroid gland is attempted [11–13]. However, the temporary interruption of anti-coagulation or anti-platelet agent can potentially elevate the risk of subsequent stroke and thrombo-embolic event, especially in the presence of non-valvular atrial fibrillation [14]. Unlike other established ablation techniques like RFA or LA, HIFU ablation is a unique form of intervention that does not require the puncture of the thyroid capsule and therefore, even with bleeding, it would be contained as all tissue planes remain intact [8,9]. Furthermore, there is currently a substantial lack of evidence and official recommendations on whether an anti-coagulation or anti-platelet agent should be withheld before a HIFU

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procedure. Based on these reasons, patients undergoing HIFU treatment generally continue their anti-coagulation or anti-platelet agent during the treatment period. However, to our knowledge, the safety of this practice has not been described in the literature. Therefore, we aimed to describe the safety and efficacy of HIFU ablation of benign nodules in patients who continued taking an anti-coagulation or anti-platelet agent in the treatment period.

Methods

This retrospective analysis was approved by local institutional review board and all patients gave informed consent before treatment. Three hundred, twenty-three consecutive patients who underwent HIFU ablation for a symptomatic, solid or predominantly-solid (<30% cystic areas), benign thyroid nodule from November 2015 to December 2017 were reviewed. Among them, 15 patients (5.1%) received two treatments in the same session while 5 (0.7%) patients were followed up <6 months. Therefore, 303 (93.8%) patients underwent single HIFU treatment with 6 months or longer follow-up. The mean age was 48.94 ± 11.95 years. The male to female ratio was 67:236 (1:3.5). The mean baseline nodule volume was 23.84 ± 25.33 ml.

After carefully weighing the benefits and the possible thrombo-embolic risk of discontinuing any anti-coagulation or anti-platelet agent at the time of treatment as well as the substantial lack of evidence in withholding one of these agents during HIFU ablation, over the study period, it was decided to not discontinue any anti-coagulation or anti-platelet agent before treatment. Among them, 12 (3.9%) patients were taking an anti-coagulation or anti-platelet agent before the ablation and continued to take it during the treatment period (group 1) while the rest ($n = 291$) were not taking any anti-coagulation or anti-platelet agent before or during treatment (group 2).

Patient selection

HIFU ablation was done only for patients who did not wish to undergo surgery. Details on patient selection for HIFU had been previously described [9,15]. In brief, the nodule had to be benign on fine needle aspiration cytology (Bethesda category II) [16] and have a low to very-low suspicion sonographic pattern [2] with its center located within the treatable depth (7–30 mm) from skin. Also, the swelling had to be causing obstructive symptoms and the longest diameter of the nodule had to be ≥ 20 mm but ≤ 60 mm on ultrasonography (US).

Study endpoints

Given that thyroid bleeding is the most relevant sequel in this setting, the primary study endpoint was the number or incidence of active thyroid bleeding, intralesional/pericapsular hematoma or subcutaneous neck bruising diagnosed during or in the first 4 days of the treatment by clinical or US examination. All patients underwent a formal US examination

of the thyroid gland and the neck immediately and 4 days after treatment (i.e., at the first clinic visit) to look for any evidence of bleeding or hematoma in and around the thyroid gland and neck. The secondary study endpoints were treatment-related complications and treatment efficacy (such as extent of nodule shrinkage and symptom score at 6-month).

Nodule shrinkage

Each nodule was measured by us on the day of treatment (baseline), 3-month and 6-month. Nodule dimensions were measured using the LOGIQ e (GE Healthcare) scanner equipped with a 10–14 MHz linear matrix transducer. Three orthogonal diameters of the index nodule (its longest diameter and two other perpendicular diameters) were measured. In general, the longest diameter was the cranio-caudal dimension (length) of the nodule while the other two perpendicular diameters were the medio-lateral (width) and antero-posterior (depth) dimensions of the nodule. All measurements were made to the nearest 0.1 mm. To estimate nodule volume, we used the formula: volume (mL) = (width (in cm) \times length (in cm) \times depth (in cm) \times ($\pi/6$)) where π was taken as 3.14159. The extent of nodule shrinkage or volume reduction ratio (VRR) was calculated based on the formula: $[\text{Baseline volume} - \text{volume at visit}] / [\text{Baseline volume}] \times 100$. Treatment success was defined as $\geq 50\%$ volume reduction at 6-month from baseline.

Symptom assessment

Pressure symptoms arising from the thyroid swelling were evaluated on a visual analog scale (VAS, 0–10) (0 = no symptoms at all; 10 = most severe symptoms) before treatment and 3- and 6-month after treatment.

HIFU treatment

The technique treatment had been described in details previously [9,15]. All treatments were performed by one person (B.H.L.) using the same US-guided HIFU device. After positioning, patients were sedated with diazepam (10–15 mg) and pethidine (50–100 mg). With US guidance, the treatment head was positioned until the entire nodule was within the treatable depth. Once the nodule had been marked on the screen, the device computer (Beamotion version no. TUS 3.2.2, Theraclion) automatically divided the nodule into multiple ablation subunits (voxels). Each voxel measured approximately 7.3 mm in thickness and 5 mm in width and received a continuous 8-s pulses of HIFU energy followed by 20–30 s of cooling time before the beam was moved to the adjacent voxel. The treatment lasted until all planned voxels were ablated. To ensure safety, nearby structures like the carotid artery, trachea, and skin were marked on the treatment screen before the start of treatment. To avoid inadvertent heat injury to important surrounding structures, the device automatically selected safety margins. A laser-based movement detector enabled immediate power interruption

Table 1. A comparison of patient baseline characteristics, treatment parameters and extent of nodule shrinkage between those who were taking an anti-coagulation or anti-platelet agent during treatment (Group 1) and those who did not take any anti-coagulation or anti-platelet agent during treatment (Group 2).

Variable	Group 1 (n = 12)	Group 2 (n = 291)	p-value
Patient characteristics			
- Age at treatment (years)	66.75 ± 8.81	48.08 ± 9.77	.001
- Sex (Male:Female)	5:7	62:229	.165
- Body weight (kg)	61.32 ± 9.20	58.23 ± 11.06	.277
- Body height (m)	1.64 ± 0.10	1.62 ± 0.078	.767
- Body mass index (kg/m ²)	25.90 ± 11.71	21.99 ± 2.83	.201
Characteristics of the index nodule			
- Side of the nodule (Right:Left)	8:4	140:151	.283
- Longest nodule diameter (cm)	4.1 ± 1.8	4.0 ± 1.5	.800
- Nodule volume at baseline (mL)	25.2 ± 28.1	23.4 ± 24.1	.853
- Distance from skin to center of nodule (cm)	1.7 ± 0.4	1.7 ± 0.4	.712
Baseline blood tests			
- Serum TSH (mIU/L)	0.94 ± 0.73	1.37 ± 0.92	.073
- Serum free T4 (pmol/L)	16.23 ± 2.55	17.54 ± 1.58	.098
- Anti-Tg autoantibody (IU/mL)	68.3 ± 14.1	91.5 ± 80.8	.076
- Anti-TPO autoantibody (IU/mL)	184.2 ± 223.6	163.8 ± 374.1	.879
Treatment parameters			
- Total energy delivered (KJ)	12.92 ± 4.39	14.79 ± 5.39	.416
- Total 'on-beam' treatment time (minutes)	43.75 ± 38.10	38.74 ± 11.45	.895
- Energy per each pulse (J)	300.39 ± 16.82	311.44 ± 26.59	.783
6-month volume reduction ratio (%)	55.96 ± 14.04	61.29 ± 17.93	.073

Continuous variables are expressed in mean ± standard deviation. Abbreviations: TSH: thyroid stimulating hormone; Anti-Tg: Anti-thyroglobulin; TPO: thyroid peroxidase. Nodule volume at baseline: (width × depth × length) × (π/6) where π was taken as 3.14159.

when the patient moved or swallowed during ablation. To avoid skin burn, the skin was cooled by a balloon (filled with 10 °C liquids) at the tip of the treatment head. Both the total amount of energy delivered to the nodule (in KJ) and the 'on-beam' (sonification) time taken (in minutes) were automatically recorded by the device. After treatment, a transcutaneous laryngeal US (TLUS) was done to assess the mobility of both vocal cords [17]. Oral diet was resumed immediately afterwards and patients were allowed to go home two hours after treatment.

Statistical analysis

Continuous variables were expressed as mean ± SD. Median and interquartile range were also presented where appropriate. Continuous variables between groups were compared using the Mann–Whitney *U* test. Chi-square tests were used to compare categorical variables. For correlation between two continuous variables, the Spearman's correlation test was performed. Based on the reported risk of bleeding/hematoma from RFA [12,13], the incidence of bleeding for group 1 and 2 were estimated to be 8 ± 5% and 2 ± 1%, respectively and so, a sample size of 12 (for group 1) and 291 (for group 2) would have had a 96% power of detecting a difference in bleeding complications between the two groups, with a significance of 0.05 using a two-sided two-sample *t*-test. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc.). All significance tests were two-tailed and those with a *p* values less than .05 were considered statistically significant.

Results

Table 1 compares the baseline characteristics and treatment parameters between group 1 and 2. Apart from the older age in group 1 (66.75 years vs. 48.08 years, *p* = .001), both

groups had comparable characteristics and treatment parameters. To our knowledge, no patients in group 2 purposely stopped anti-coagulation or anti-platelet agent during treatment and no patients in both groups suffered a preexisting bleeding tendency or coagulopathy problem. The reason for and the dose/type of the anti-coagulation or anti-platelet therapy for group 1 are shown in **Table 2**. For group 1, the majority of patients (58.3%) were placed on an anti-platelet agent (i.e., daily Aspirin with dose ranging between 80–100 mg) for history of ischemic heart disease. The other 5 (41.7%) patients were put on an anti-coagulation agent (i.e., Warfarin or Rivaroxaban) for valvular heart disease (*n* = 2), non-valvular atrial fibrillation (*n* = 2) and pulmonary embolism (*n* = 1).

Treatment efficacy

At baseline, the mean nodule volume was 25.3 ± 28.0 ml. At 3-month after treatment, the mean volume was reduced to 16.0 ± 22.9 ml. The mean 3-month VRR in group 1 and 2 were 46.1 ± 16.3% and 51.8 ± 19.4%, respectively (*p* = .253). Exactly half of the group 1 patients (50.0%) achieved treatment success while 156 (53.6%) in group 2 achieved treatment success at 3-month (*p* = .738). The 6-month mean VRR in group 1 and 2 were 56.0 ± 14.0% and 61.3 ± 17.9% (*p* = .073).

Pressure symptoms as rated by VAS at baseline, 3-month and 6-month did not significantly differ in group 1 and 2 (*p* > .05). At baseline, the VAS in group 1 and 2 were 6.33 ± 1.37 and 5.94 ± 2.70, respectively (*p* = .372). At 3-month, the VAS in group 1 and 2 were 2.42 ± 0.79 and 2.94 ± 0.74, respectively (*p* = .531) and at 6-month, the VAS in group 1 and 2 were 1.25 ± 0.87 and 1.60 ± 2.00, respectively (*p* = .193). In group 1, pressure symptoms were significantly reduced from 6.33 ± 1.37 (median = 6.0; IQR = 1.75) at baseline to 2.42 ± 0.79 (median = 2.0; IQR = 1.0) at 3-month (*p* < .001) and to 1.25 ± 0.87 (median = 1.5; IQR = 1.8) at 6-

Table 2. Medical comorbidities and type/dose of anticoagulation or antiplatelet agent during treatment in group 1.

Patient number	Age/Sex	Medical comorbidities at the time of ablation	Type and dose of anticoagulation or antiplatelet agent during ablation	Nodule volume (mL)		Treatment-related complications
				Initial	6-month	
1	57/Male	Aortic valve replacement	Warfarin 3 mg daily	16.8	9.5	None
2	76/Female	IHD, hyperlipidemia, DM, PVD with toe ulcers	Aspirin 80 mg daily	8.4	4.6	None
3	51/Female	IHD, 1st-degree heart block, HT	Aspirin 100 mg daily	7.8	2.8	None
4	59/Male	IHD with PCI, hyperlipidemia	Aspirin 80 mg daily	13.5	5.4	None
5	77/Female	IHD, DM, PVD with foot ulcers	Aspirin 80 mg daily	16.5	5.9	None
6	80/Female	HT, AF, chronic heart block	Rivaroxaban 15 mg daily	108.7	62.9	None
7	67/Female	HT, AF	Rivaroxaban 15 mg daily	11.3	2.1	None
8	68/Female	IHD, DM, hyperlipidemia	Aspirin 80 mg daily	9.3	3.4	None
9	59/Male	Aortic valve replacement	Warfarin 2.5 mg daily	17.3	5.3	None
10	69/Male	DM, HT, hyperlipidemia, IHD with PCI	Aspirin 100 mg daily	23.2	11.3	None
11	71/Female	PE / DVT	Warfarin 3 mg daily	28.4	12.5	None
12	67/Male	IHD, DM, HT	Aspirin 80 mg daily	42.1	29.3	None

Abbreviations: IHD: ischemic heart disease; DM: diabetes mellitus; PVD: peripheral vascular disease; HT: hypertension; PCI: percutaneous cardiac intervention; PE: pulmonary embolism; DVT: deep vein thrombosis. Nodule volume = (width × depth × length) × (π/6) where π was taken as 3.14159.

month ($p < .001$). Also, there was a significant inverse correlation between VRR at 6-month and VAS at 6-month ($p = .842$, $p = .001$) (implying that a greater the extent of shrinkage was associated with a lower VAS score at 6-month).

Safety and complications

Active thyroid bleeding, intralesional/pericapsular hematoma or subcutaneous neck bruising were not evident in either group during or 4 days after treatment by clinical or US examination. The incidence of skin redness and minor swelling immediately afterward in group 1 and 2 were 8 (66.7%) and 183 (62.9%), respectively ($p = .362$). They all settled within the first week. On TLUS, nobody in group 1 suffered from a vocal cord paresis while 3 (1.0%) patients in group 2, 2 suffered from vocal cord paresis afterward ($p = .381$). No patients (0.0%) in group 1 suffered from any other treatment-related complications like Horner's syndrome or skin burn and two (0.7%) patients in group 2 suffered from temporary Horner's syndrome ($p = 1.000$).

Discussion

To our knowledge, this is the first report to examine the safety and efficacy of HIFU ablation in patients who continued to take an anti-coagulation or anti-platelet agent during the treatment period. The reason for studying this particular patient subgroup is because bleeding and hematoma are not at all uncommon following any form of instrumentation or procedure to the thyroid gland, irrespective of the magnitude of the intervention [5,10–13] and patients who continue taking an anti-coagulation or anti-platelet agent are at risk of bleeding complications [18]. Despite being a minimally invasive treatment with low overall complication rates, potentially life-threatening complications like thyroid rupture and abscess formation resulting from bleeding have been reported from thermal ablation of benign thyroid nodules [19–21]. The key message of the

present study is that it seems to be safe and feasible to continue an anti-coagulation or anti-platelet agent in HIFU ablation of benign thyroid nodules. In addition, treatment efficacy remains comparable to those not taking any anti-coagulation or anti-platelet agent. Although this was a relatively small patient series with only 12 of the 303 patients eligible for analysis, it is worth highlighting that not even mild bleeding or intralesional/pericapsular hematoma were detectable on US examination during or in the first 4 days of treatment. Despite the small patient cohort, we believe this was largely attributed to the fact that in HIFU ablation, all tissue planes around the gland remained uninterrupted and therefore, the risk of in or around the thyroid gland if any during or after treatment was extremely low. The clinical relevance is that in the future, HIFU ablation should be considered an ablation technique especially for patients who might be too ill to discontinue an anti-coagulation or anti-platelet agent in the treatment period or at a significant risk of thrombo-embolic event when an anti-coagulation or anti-platelet agent is discontinued even for a short period of time.

Apart from safety, it should be highlighted that HIFU ablation continued to be efficacious in this patient subgroup as those not taking anti-coagulation or antiplatelet agent. There appeared to be no or little impact on the extent of nodule shrinkage or improvement in symptoms when continuing an anti-coagulation or anti-platelet agent. Relative to our previously reported series, the present treatment efficacy appeared comparable and there was a significant correlation between the extent of nodule shrinkage and severity of symptom score 6-months after treatment [9,15].

Despite these findings, we would like to acknowledge the fact that this was a small observational study with only around 4% of patients actually requiring an anti-coagulation or anti-platelet agent before treatment. Therefore, to fully resolve the question of safety and feasibility, a larger prospective study will be required.

Conclusion

HIFU ablation is a safe and efficacious thermal ablation technique in patients who continued to take an anti-coagulation or anti-platelet agent in the treatment period. Based on these findings, HIFU seems to be feasible in patients who continue to take an anti-coagulation or anti-platelet agent in the treatment period.

Acknowledgment

We would like to thank Mr. Hill YU and Ms. LI Wing Kar for conducting all the symptom (or VAS score) assessments for the entire study period.

Disclosure statement

All authors had nothing to disclose. No competing financial interests exist.

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