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ULTRASOUND

Effect of perithyroidal lignocaine infusion (PLI) to pain experienced during high-intensity focused ultrasound (HIFU) ablation of benign thyroid nodules

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Abstract

Objective To assess whether perithyroidal lignocaine infusion (PLI) could provide additional analgesia in high-intensity focused ultrasound (HIFU) treatment of benign thyroid nodules for patients already receiving their usual intravenous doses of Pethidine and Diazemuls.

Methods Two hundred and five patients who underwent HIFU ablation for a benign thyroid nodule were analyzed. Among them, 104 (50.7%) patients received PLI in addition to their boluses of Pethidine and Diazemuls before treatment (group I), while the rest ($n = 101$, 49.3%) received intravenous Pethidine and Diazemuls only (group II). After treatment, patients were asked to rate their overall pain experience on a visual analogue scale (VAS) (0–100) (0, no pain; 100, worse possible pain) during treatment. Binary logistic regression was performed to evaluate significant determinants for treatment pain including demographics, doses of medications, and treatment parameters.

Results VAS was significantly lower in group I (51.30 vs. 63.79, $p = 0.002$). In the multivariate analysis, older age at treatment (OR = 1.036, 95%CI = 1.008–1.065, $p = 0.011$), lower BMI (OR = 1.202, 95%CI = 1.083–1.334, $p = 0.001$), higher Diazemuls dose (OR = 1.066, 95%CI = 1.018–1.114, $p = 0.006$), and use of PLI (OR = 2.096, 95%CI = 1.121–3.922, $p = 0.020$) were independent determinants of less treatment pain.

Conclusions PLI can provide additional analgesia in patients already receiving their usual intravenous doses of Pethidine and Diazemuls during HIFU ablation of benign thyroid nodules. Older age, lower body mass index, and greater Diazemuls (i.e., a sedative) dose are significantly associated with less treatment pain.

Key Points

- *PLI provided an additional analgesic effect in HIFU ablation of thyroid nodules.*
- *Older age and lower BMI were significantly associated with less pain.*
- *Higher doses of Diazemuls lessened pain during HIFU ablation.*

Keywords Interventional ultrasonography · High-intensity focused ultrasound ablation · Pain management · Nodular goiter · Ablation techniques

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Abbreviations

BMI	Body mass index
HIFU	High-intensity focused ultrasound
PLI	Perithyroidal lignocaine infusion
RFA	Radiofrequency ablation
US	Ultrasonography
VAS	Visual analogue scale
VRR	Volume reduction ratio

Introduction

Thyroid nodules are common. Although most are benign and will remain relatively unchanged over time, some can become large and cause symptoms [1–3]. When this happens, surgery is usually required [1, 2]. However, surgery is not without risks and requires a general anesthesia and hospitalization. As a result, there has been a growing interest in developing less invasive, non-surgical techniques in treating benign thyroid nodules [4–6]. For predominantly solid or solid nodules, several thermal ablation techniques such as laser, microwave, and radiofrequency ablation (RFA) have been shown to be effective [4–6]. High-intensity focused ultrasound (HIFU) is one of the newer techniques which has been shown to be effective in inducing nodule shrinkage and alleviating nodule-related symptoms [7–10].

However, HIFU ablation to the thyroid gland is not a painless procedure, and at times, the pain can be so severe that the procedure has to be stopped prematurely [11]. The other problem with inadequate pain control is that it can result in involuntary neck movements, which in turn, can cause inaccurate sonication of the target, leading to lower treatment efficacy [12]. Therefore, good pain control is essential but the best analgesic and anesthetic regimen for HIFU ablation remains unclear [11]. In our experience, boluses of intravenous Pethidine and Diazemuls were able to provide reasonable pain management during HIFU ablation [12].

Infusion of lignocaine (a local anesthetic) into the perithyroidal space on the treatment side (or in short, perithyroidal lignocaine infusion (PLI)) is another method that may reduce pain further. Although it is commonly utilized in RFA and laser ablation [13–15], its role in HIFU ablation has yet to be established. As a result, the present study aimed to see whether PLI could provide an additional analgesic effect (i.e., less pain reported) during HIFU treatment of benign thyroid nodules in patients who were already receiving their usual doses of Pethidine and Diazemuls.

Methods

This retrospective analysis was approved by the local institutional review board. All relevant clinical and treatment data were recorded prospectively after obtaining informed consent from patients. Consecutive patients who underwent HIFU ablation for a symptomatic, solid or predominantly solid (< 30% cystic areas), benign thyroid nodule from August 2015 to November 2017 were analyzed. During this period, all patients received one bolus of intravenous Diazepam (10 mg) and Pethidine (50 mg) before the start of the procedure. Additional boluses were given during treatment when the effect of these drugs began to wear off. The accumulative amounts of drugs given were recorded prospectively. To further improve pain control, from October 2016, PLI was given in addition to the usual boluses of Pethidine and Diazemuls. The technical details of PLI had been described previously [14]. In short, a standard 21G needle was inserted from the midline of the anterior neck with the tip angled parallel to the thyroid capsule and slowly advanced toward the side of the ablation site under ultrasound (US) guidance. Once the tip had been positioned next to the thyroid capsule, 10 mL of 2% lignocaine was infused into the perithyroidal space (Fig. 1). Treatment (i.e., the first HIFU pulse) generally began 5–7 min after the infusion. During treatment, the patients' heart rate, blood pressure, respiration rate, and peripheral oxygenation were continuously monitored. Any side effects including those related to lignocaine toxicity were carefully sought. During treatment, patients were asked to make a hand sign if the pain became intolerable. To lessen the pain, at times, either the power was lowered or more intravenous boluses were administrated and this practice remained unchanged for the entire study period. No analgesia was routinely prescribed after treatment. Upon completion of treatment, patients were asked to rate their overall (global) pain experience during treatment (T1), 2 h after treatment (T2), and the following morning (T3). Pain level was scored on a visual analogue scale (VAS) from 0 to 100 (0, no pain at all; 100, worse possible pain) by one dedicated person not directly involved with the study. The primary study endpoint was pain score at T1 while pain scores at T2 and T3 were secondary endpoints. To assess whether there was a possible association between overall pain during treatment (pain at T1) and baseline patient characteristics and treatment parameters, patients were categorized into those below and those above the median of pain score at T1.

Case selection

At our institution, only patients who required but refused surgery were considered for ablation. Details on the eligibility for ablation were previously described [9, 12]. In short, only

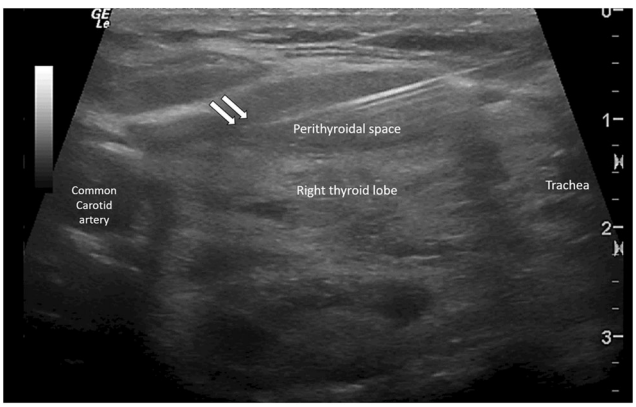

Fig. 1 Ultrasound image taken at the time of perithyroidal lignocaine infusion (PLI) with the tip of the needle (marked by arrows)

nodules proven to be benign on fine-needle aspiration cytology (Bethesda category II) with its center measured within 5–30 mm from the skin were eligible for HIFU ablation. The nodule of interest had to have all three orthogonal dimensions ≥ 20 mm but ≤ 50 mm on US. For the present study, only patients who had only one treatment applied to a single nodule were analyzed. Any patients with missing pain data during or after HIFU treatment, had two nodules treated in the same session, or two treatments applied to the same nodule were excluded.

HIFU treatment

All treatments were performed by one person (B.H.L) using the same commercially available US-guided HIFU device. Patients were placed in a supine position with the neck slightly extended. All ablations began at 256 J per pulse and increased slowly until hyperechoic marks (i.e., US-stimulated microbubbles at the focal point) appeared on the treatment screen (Fig. 2). The US-guided HIFU device comprised an energy generator, a treatment head, a skin-cooling device, and a touch screen interface for planning. The treatment head incorporated an image transducer (7.5 MHz, 128 elements, linear array) and HIFU transducer (3 MHz, single element, 60 mm in diameter). The device computer (Beamotion version no. TUS 3.2.2, Theraclion) automatically divided the nodule into multiple ablation voxels. Each voxel measured approximately 7.3 mm in thickness and 5 mm in width and received a continuous 8-s pulse of HIFU energy followed by 30–40 s of cooling time before the beam was moved to the adjacent voxel. To ensure safety, nearby structures like the carotid artery, trachea, and skin were marked out on the treatment screen before the start of treatment by the operator. To avoid inadvertent heat injury to important surrounding structures, the device automatically selected the following safety margins, (a) 0.5 cm from the skin, (b) at least 0.5 cm from the trachea and recurrent laryngeal nerve, and (c) 0.2 cm from the ipsilateral carotid artery, and canceled any voxels which were within these distances. A laser-based movement detector enabled immediate power interruption 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" (sonication) time taken (in minutes) were automatically recorded by the device's computer. Oral diet was resumed immediately afterward and patients were discharged home a few hours after treatment.

Treatment efficacy

Each nodule was measured by US on the day of treatment (baseline) and 3, 6, and 12 months after treatment (Fig. 3). Nodule dimensions were measured using the LOGIQ e

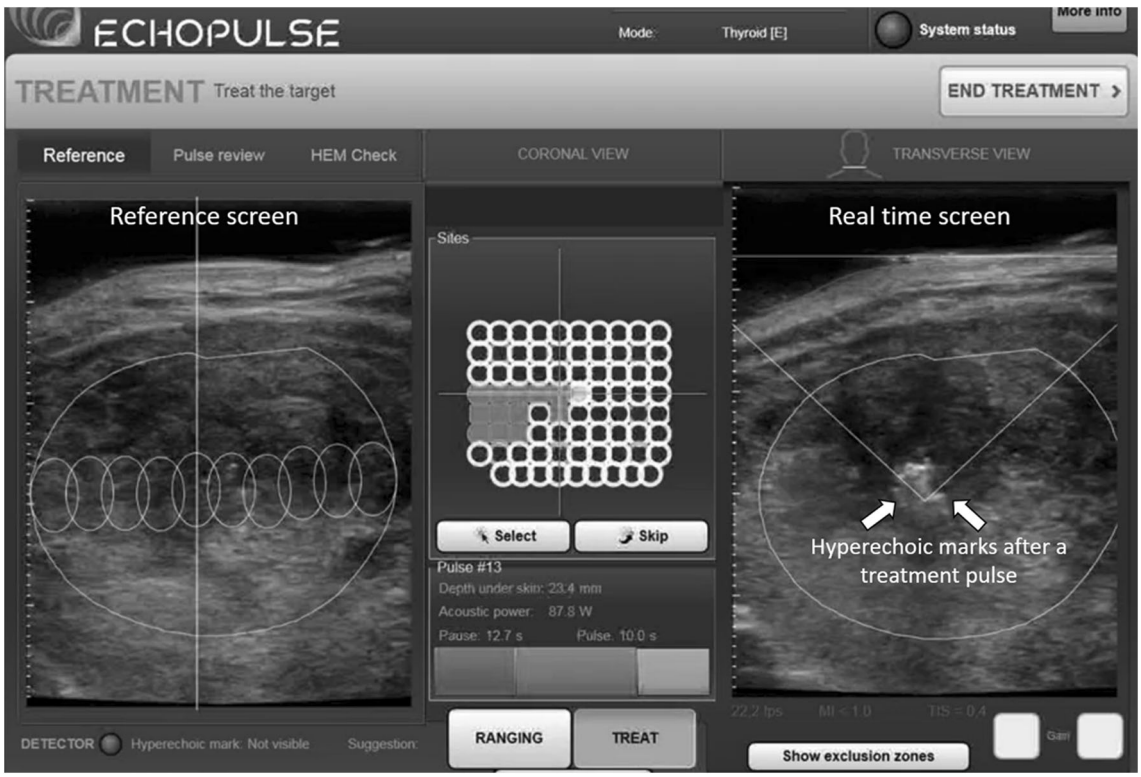

Fig. 2 A picture of the treatment screen captured immediately after an 8-s treatment pulse. Note the presence of hyperechoic marks at the ablated area

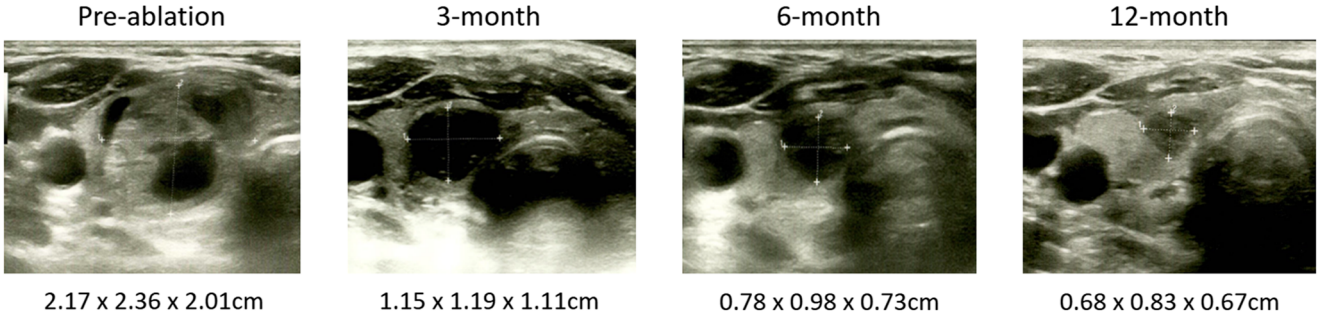

Fig. 3 Ultrasound pictures of a right thyroid nodule before and 3, 6, and 12 months after ablation

(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) × length (in cm) × depth (in cm)) × (π/6) where π was taken as 3.14159. The volume reduction ratio (VRR) was calculated based on the formula: [Baseline volume – volume at visit]/[Baseline volume] × 100. Treatment success was defined as ≥ 50% volume reduction at 6 months from baseline.

Laboratory methods

All measurements of TSH, FT4, and anti-thyroid autoantibodies were carried out at our institution's laboratory. Plasma TSH was determined by a specific two-site immunometric assay (Eleosys 2010). Serum anti-Tg and anti-TPO autoantibodies were determined by radioimmunoassay (Bio Code).

Statistical analysis

Continuous variables were generally expressed as mean ± SD. Median and range were also presented when 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. Binary logistic regression model was performed to identify independent factors for less pain. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc.). All significance tests were two-tailed and those with a p value less than 0.05 were considered statistically significant.

Results

A total of 230 patients completed HIFU ablation of benign thyroid nodule. Of these, 12 (5.2%) patients had missing pain scores during or after treatment while 13 (5.7%) patients received two sequential HIFU treatments in the same session. After excluding these patients, 205 (89.1%) patients were eligible for analysis. Among them, 104 (50.7%) patients received PLI on top of their boluses of Pethidine and Diazemuls before the treatment (group I), while the rest (n = 101, 49.3%) received intravenous boluses of Pethidine and Diazemuls only (group II).

At T1, patients reported an overall mean (± SD) pain score of 57.39 ± 29.78, while the median (range) was 65.0 (0.00–100.00). Twenty-eight (13.7%) had a pain score of 0.00. At T2, the mean (± SD) pain score dropped significantly to 26.67 ± 24.70 (p < 0.001) with a median (range) of 25.00 (0.00–90.00). Sixty-five (31.7%) patients had a pain score of 0.00. At T3, the mean (± SD) pain score dropped even further, from baseline to 15.87 ± 18.43 (p < 0.001) with a median (range) of 10.00 (0.00–75.00). Eighty-one (39.5%) patients had a pain score of 0.00. Pain score at T1 significantly correlated with pain score at T2 (ρ = 0.414, p < 0.001) and at T3 (ρ = 0.359, p < 0.001). None of the patients complained of nausea or vomiting afterwards or had any manifestations of lignocaine toxicity. All were able to be discharged home 3–4 h after treatment.

Baseline characteristics, treatment parameters, and efficacy were compared between group I and group II (Table 1). Patient age at treatment, sex ratio, body mass index (BMI), longest nodule diameter, baseline nodule volume, distance from skin to nodule center, thyroid function, and level of thyroid autoantibodies were similar between the two groups (p > 0.05). However, patients in group I had significantly shorter total "on-beam" treatment time than those in group II (39.60 min vs. 43.42 min, p = 0.039) and slightly fewer treated sites (46.94 vs. 52.63, p = 0.182). These might be related to the slightly smaller baseline nodule volume (24.19 mL vs. 26.88 mL, p = 0.483) as total on-beam time correlated significantly with baseline nodule volume (ρ = 0.418, p < 0.001). Interestingly, group I received a significantly lower mean dose of Pethidine (78.13 mg vs. 87.18 mg, p = 0.001) but a higher mean dose of Diazemuls (14.78 mg vs. 12.47 mg, p < 0.001)

Table 1 A comparison of baseline characteristics, treatment parameters, efficacy, and pain score between those who received lignocaine infiltration (group I) and those who did not (group II) prior to high intensity focused ultrasound (HIFU) ablation treatment

Variable	Group I ($n = 104$)	Group II ($n = 101$)	p value
Patient characteristics			
- Age at treatment (years)	46.52 ± 11.52	48.58 ± 11.35	0.147
- Sex (male:female)	13:91	16:85	0.492
- Body mass index (kg/m^2)	22.62 ± 4.02	24.22 ± 3.69	0.084
Nodule characteristics			
- Longest nodule diameter (cm)	4.17 ± 1.23	4.03 ± 1.29	0.440
- Nodule volume at baseline* (mL)	24.19 ± 24.28	26.88 ± 29.96	0.483
- Distance from skin to nodule center$^+$ (cm)	1.76 ± 0.26	1.76 ± 0.35	0.622
Baseline blood tests			
- Serum TSH (mIU/L)	1.50 ± 2.20	1.45 ± 2.71	0.659
- Serum free T4 (pmol/L)	16.85 ± 3.97	16.87 ± 3.48	0.981
- Anti-Tg autoantibody (IU/mL)	427.26 ± 976.01	273.83 ± 675.96	0.313
- Anti-TPO autoantibody (IU/mL)	1168.43 ± 2080.11	1087.58 ± 2322.96	0.476
Treatment parameters			
- Total energy delivered (kJ)	14.57 ± 4.62	14.52 ± 5.57	0.471
- Total "on-beam" time (minutes)	39.60 ± 9.21	43.42 ± 11.55	*0.039*
- Energy per each pulse (J)	303.00 ± 29.62	299.42 ± 30.75	0.754
- Effective power per pulse (watts)	39.69 ± 3.76	39.58 ± 4.34	0.746
- Number of treated sites	46.94 ± 16.38	52.63 ± 17.42	0.182
Total amount of medications administered			
- Intravenous Pethidine (mg)	78.13 ± 22.69	87.18 ± 24.59	*0.001*
- Intravenous Diazemuls (mg)	14.78 ± 4.42	12.47 ± 8.48	*< 0.001*
Treatment efficacy (%)			
- 3-month VRR	51.25 ± 17.54	55.90 ± 18.23	0.242
- 6-month VRR	63.09 ± 22.27	69.58 ± 17.59	0.433
- 12-month VRR	65.17 ± 20.39	69.19 ± 18.38	0.783
Pain score by VAS (0–100)			
- During treatment (T1)	51.30 ± 30.31	63.79 ± 27.96	*0.002*
- Two hours after treatment (T2)	28.32 ± 22.13	31.88 ± 25.98	0.098
- The next morning (day 1) (T3)	13.86 ± 16.38	17.64 ± 19.99	0.277

Continuous variables are expressed in mean ± standard deviation. Italicized data signify statistical significance

Abbreviations: *TSH*, thyroid-stimulating hormone; *Anti-Tg*, anti-thyroglobulin; *TPO*, thyroid peroxidase; *VRR*, volume reduction ratio; *VAS*, visual analogue scale (0–100)

*Nodule volume at baseline = (width × depth × length) × (π/6) where π was taken as 3.14159

$^+$ Perpendicular distance measured from the baseline ultrasonography

than group II. In terms of treatment efficacy, the 3-, 6-, and 12-month VRR were comparable between the two groups ($p > 0.05$). For group I, the mean pain score at T1 was significantly lower than group II (51.30 vs. 63.79, $p = 0.002$), while there was also a tendency for lower pain scores at T2 and T3 (28.32 vs. 31.88, $p = 0.098$, and 13.86 vs. 17.64, $p = 0.277$, respectively) (Fig. 4).

In the univariate analysis by logistic regression (Table 2), older age at treatment (OR = 1.026, 95%CI = 1.001–1.052, $p = 0.045$), lower BMI (OR = 1.157, 95%CI = 1.060–1.263, $p = 0.001$), higher Diazemuls dose (OR = 1.067, 95%CI = 1.022–1.114, $p = 0.003$), and use of PLI (OR = 1.927, 95%CI = 1.103–3.367, $p = 0.021$) were significantly associated with pain score at T1 ≤ 65.0.

In the multivariate analysis, when all significant factors from univariate analysis were entered simultaneously (Table 3), it was found that older age at treatment (OR = 1.036, 95%CI = 1.008–1.065, $p = 0.011$), lower BMI (OR = 1.202, 95%CI = 1.083–1.334, $p = 0.001$), higher Diazemuls dose (OR = 1.066, 95%CI = 1.018–1.114, $p = 0.006$), and use of PLI (OR = 2.096, 95%CI = 1.121–3.922, $p = 0.020$) were independent factors for pain score at T1 ≤ 65.0.

Using the median of 47.0 years old as cutoff for age, those aged ≤ 47.0 years old were significantly less likely to report a

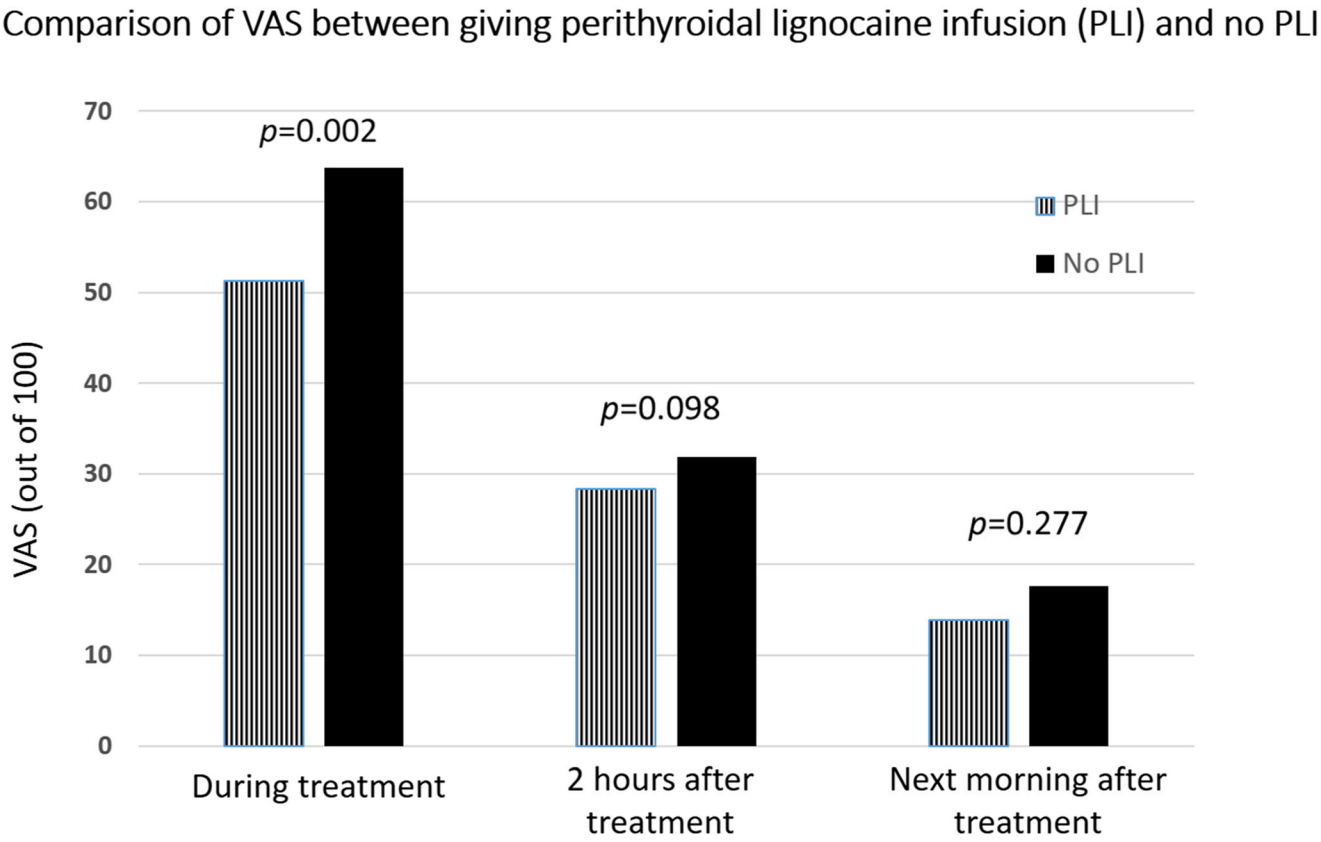

Fig. 4 A bar chart showing the association between giving perithyroidal lignocaine infusion (PLI) and not giving PLI on pain scores during treatment, 2 h after treatment, and the next morning after treatment

pain score at T1 ≤ 65.0 than those aged > 47 years old (44.2% vs. 59.3%, $p = 0.043$). Using the median of 22.4 kg/m^2 as the cutoff for BMI, those with BMI ≤ 22.4 kg/m^2 were significantly more likely to report a pain score at T1 ≤ 65.0 than those with BMI > 22.4 kg/m^2 (60.0% vs. 42.8%, $p = 0.013$). Patients with a BMI > 22.4 kg/m^2 reported significantly higher pain score at T1 and at T2 than patients with a BMI ≤ 22.4 kg/m^2 ($p = 0.044$ and $p < 0.001$, respectively). Similarly, using the median of 10.0 mg as the cutoff for Diazemuls dose, those who received a total dose of ≥ 10.0 mg were significantly more likely to report a pain score at T1 ≤ 65.0 than those who received < 10 mg (56.0% vs. 31.8%, $p = 0.005$). Patients who received PLI were significantly more likely to report pain score at T1 ≤ 65.0 (58.7% vs. 42.4%, $p = 0.021$).

Discussion

The most important finding of the present study was that PLI provided additional analgesia in patients already receiving the usual boluses of Pethidine and Diazemuls. Group I patients reported lower pain score during treatment than group II (51.30 vs. 63.79, $p = 0.002$), and in the regression model, PLI was significantly associated with less treatment pain (OR = 2.096, 95%CI = 1.121–3.922, $p = 0.020$). Given that there were virtually no side effects from PLI administration, we recommend that PLI should be performed as a routine for HIFU ablation.

Pain management in HIFU ablation has been a controversial subject with little consensus on what should be the best analgesic and anesthetic regimen. It is clear that the type of anesthetic or analgesic medications administered during ablation can vary greatly between institutions [7–10, 12, 16, 17]. A group of investigators recently reported successful ablation with no anesthesia or sedation when the sonication power was set in the low range [10]. However, with a higher power setting, stronger analgesia and anesthetic agents might be necessary [12, 18].

Another finding worth highlighting was that there were significant differences in Pethidine ($p = 0.001$) and Diazemuls ($p < 0.001$) used between the two groups. We believe these findings were attributed to a subtle change in drug administration with the operator being more inclined to use a higher dose of Diazemuls (a benzodiazepine) while lowering the doses of Pethidine (an opioid). With increased experience, we believe the treatment pain could be significantly mitigated by increasing the dose of Diazemuls (i.e., a sedative) relative to that of Pethidine (an analgesia).

Another finding worth highlighting was that age at treatment was an independent determinant of pain during treatment (OR = 1.036, 95%CI = 1.008–1.065, $p = 0.011$). Younger patients (age < the median) were significantly less likely to report

Table 2 A univariate analysis of factors leading a lower pain score (VAS ≤ 65/100) during high-intensity focused ultrasound (HIFU) ablation treatment

Variable	ß-coefficient	Odds ratio (95%CI)	*p* value
Older age at treatment (years)	0.250	1.026 (1.001–1.052)	*0.045*
Male sex^	0.223	1.553 (0.700–3.448)	0.249
Lower body mass index (kg/m^2)	0.146	1.157 (1.060–1.263)	*0.001*
Longer nodule diameter (cm)	0.209	1.233 (0.927–1.639)	0.151
Larger nodule volume at baseline (mL)	0.007	1.007 (0.992–1.021)	0.350
Longer distance from skin to nodule center (cm)	0.357	1.429 (0.431–4.739)	0.559
Higher serum TSH (mIU/L)	0.060	1.062 (0.940–1.199)	0.333
Less total energy delivered (kJ)	0.018	1.018 (0.963–1.076)	0.901
Less energy per treatment pulse (J)	0.004	1.004 (0.994–1.013)	0.430
Shorter "on-beam" treatment time (minutes)	0.005	1.005 (0.981–1.030)	0.664
Higher Pethidine dose (mg)	0.001	1.001 (0.989–1.012)	0.901
Higher Diazemuls dose (mg)	0.065	1.067 (1.022–1.114)	*0.003*
Use of PLI^	0.655	1.927 (1.103–3.367)	*0.021*

Italicized data signify statistical significance

Abbreviations: *TSH*, thyroid-stimulating hormone; *VAS*, visual analogue scale (0–100); *PLI*, perithyroidal lignocaine infusion

^Entered as a categorical variable into the regression model

lower pain than older patients (44.2% vs. 59.3%, $p = 0.043$). One reason might be because older patients tend to metabolize both Pethidine and Diazemuls more slowly and are more sensitive to the effects of the drug, even at similar blood plasma levels [19]. As a result, perhaps, in the future, younger patients could receive higher doses of intravenous medications.

On a similar note, the fact that patients with lower BMI reported less pain during treatment could be explained by the pharmacokinetic differences between high and low BMI patients [20, 21]. Given that Diazemuls is highly lipid soluble and is widely distributed throughout the body after administration, a patient with a lower BMI would require much lower doses of Diazemuls to have the same anesthetic effect. As a result, our data showed that patients below the median BMI were significantly more likely to report lower pain score than those above the median BMI. This finding was similar to that of our previous study [12].

Table 3 A multivariate analysis for a lower pain score (VAS ≤ 65/100) during high-intensity focused ultrasound (HIFU) ablation treatment

Variable	ß-coefficient	Odds ratio (95%CI)	*p* value
Older age at treatment (years)	0.036	1.036 (1.008–1.065)	*0.011*
Lower body mass index (kg/m^2)	0.184	1.202 (1.083–1.334)	*0.001*
Higher Diazemuls dose (mg)	0.064	1.066 (1.018–1.114)	*0.006*
Use of PLI	0.739	2.096 (1.121–3.922)	*0.020*

Italicized data signify statistical significance

Abbreviation: *VAS*, visual analogue scale; *PLI*, perithyroidal lignocaine infusion

Despite these findings, we would like to acknowledge several shortcomings. First, since this was a non-randomized study, factors other than PLI and medications could have influenced pain level over time. To minimize study confounders, we tried to keep our practice (like the need for lowering the power and giving additional boluses of analgesia and anesthetic) the same throughout the entire study period. We believe the present study could pave the way for a larger randomized study looking at PLI in HIFU ablation. Second, it would be interesting to evaluate not only the severity of pain during and after treatment but also other effects (such as hangover symptoms) from our regimen in the few days after treatment.

Conclusion

PLI provided an additional analgesic effect in patients already receiving the usual doses of Pethidine and Diazemuls during HIFU ablation of benign thyroid nodules. Older patients and patients with a lower BMI significantly experienced less pain during ablation. Increasing the dose of Diazemuls (i.e., a sedative) could increase the comfort of the procedure. These findings have important implications on how to best select patients for ablation and how to best manage their pain during ablation.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Professor Stephen Cheng (Head of Department).

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Observational
- Single institution

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