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ORIGINAL SCIENTIFIC REPORT

Effects of Regional and General Anesthesia on the Therapeutic Outcome of Benign Thyroid Nodules Treated with High Intensity Focused Ultrasound (HIFU)

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Abstract

Background The study investigated whether anesthesia performed during high-intensity-focused-ultrasound treatment (HIFU) of benign thyroid nodules influenced the therapy outcome, based on volume reduction and the amount of energy delivered.

Methods Thirty patients with benign thyroid nodules were treated with HIFU under general or regional anesthesia at two centers from 2014 to 2019. During HIFU, a therapeutic ultrasound probe, EchoPulse (Teraclion, Malakoff, France), heats the focus to 80–90 degrees Celsius. Nodal volumes were measured by ultrasound before and 3 months after therapy. For statistical analysis, the total population was divided into two groups according to the anesthesia performed. In a retrospective long-term multicenter study, volume reduction and the energy delivered were analyzed using the Wilcoxon signed-rank test and the Mann–Whitney test.

Results At three months follow-up, the total study population had an average volume reduction of 39.26% (range 4.03–91.16%, $p < 0.001$, $n = 30$), the general anesthesia group of 47.46% (range 13.64–91.16%, $p = 0.001$, n = 15) and the regional anesthesia group of 31.06% (range 4.03—68.63%, $p = 0.001$, $n = 15$). Under regional anesthesia a median energy of 3.16 kJ/cm^3 (range: 0.96 – 8.2 kJ/cm^3) and under general anesthesia a median energy of 0.88 kJ/cm^3 (range: 0.18 – 1.63 kJ/cm^3) were delivered. All results were significant with $p < 0.05$. The complication rate was 6.67%.

Conclusion HIFU is an effective method to treat benign thyroid nodules. Comparing anesthesia methods, volume reduction is higher in patients treated under general anesthesia and less energy has to be delivered under general anesthesia.

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Introduction

There is a high prevalence of thyroid nodules, 50% in females and 30% in males. [1, 2]. Most benign nodules do not cause symptoms and can be easily diagnosed by ultrasound [3–5].

Therapy is performed when symptoms (sensation of pressure, dyspnea, thyrotoxicosis) or cosmetic impairment occur. Typically, nodules are treated by surgical excision or radioiodine therapy (RIT) [3, 5]. Potential side effects of these therapies are hypothyroidism, infection, hemorrhage, injury to the parathyroid gland and recurrent laryngeal nerve due to surgical removal of the nodules, and hypothyroidism due to RIT [6, 7]. RIT cannot be performed on pregnant females or on females with a desire to have children in the next few months [8]. Minimally invasive thermal ablation such as microwave ablation (MWA), radiofrequency ablation (RFA), laser and HIFU offer an alternative to surgical excision and RIT and are already used clinically. Among the minimally invasive thermal ablation procedures, HIFU is the least invasive and most precise [9]. In HIFU, a concave ultrasound probe is used to focus the ultrasound beams. The tissue is heated up to 85 degrees Celsius. The heat irreversibly causes coagulation necrosis and the nodule atrophies [5, 9–12]. Since HIFU does not penetrate the skin, it is more comfortable than traditional thyroid surgery and there is no risk of infection. It is not only used in thyroid nodule therapy, but also in prostate cancer, uterine fibroids, liver metastases, and bone metastases. [13–15] Studies have shown that HIFU is a safe and effective procedure to treat benign thyroid nodules [5, 9–12, 16, 17]. However, more evidence is needed [1].

In the present study, the effects of two anesthetic procedures on nodule volume reduction and on required energy delivery during HIFU were investigated in a multicenter study. The aim of the study is to compare volume reduction under regional anesthesia and general anesthesia in the treatment of benign thyroid nodules with HIFU and to assess whether one of the anesthesia methods is preferable during HIFU.

Materials and methods

Study design

The study is a retrospective analysis of data in an open-label study.

Patients and baseline assessment

For patient characteristics see Table 1. Patients with symptomatic benign thyroid nodules causing thyrotoxicosis, swallowing problems, pain, or hoarseness and non-symptomatic benign thyroid nodules causing cosmetic impairment were included in the study. Only patients who refused surgery or RIT of the nodules or had contraindications to the same were included. Only proven nonmalignant nodules were included.

Patients with asymptomatic nodules, malignant nodules, nodules with retrosternal growth, and nodules in proximity to sensitive structures such as the trachea, esophagus, the recurrent laryngeal nerve and the carotid artery were excluded from the study. Patients with nerve anomalies were excluded from the study.

Patients were assigned to anesthesia methods based on the in-house guidelines of the center and patients' preferences. Patients were treated with regional anesthesia at Center 1 and predominantly under general anesthesia at Center 2. There were no volume cut-offs of the nodules that influenced group selection.

All patients underwent a pre-interventional calcitonin measurement and thyroid hormone measurement. If necessary, a fine-needle aspiration biopsy (FNAB) was done to exclude malignancy. All nodules were also examined for position, volume, and echogenicity by B-mode ultrasound (Sonix Touch Ultrasound System, Ultrasonix Medical Corporation, Richmond Canada) before and at regular intervals after therapy.

A follow-up of the symptoms by means of a symptom score was not performed due to too high subjectivity. Since the volume reduction of the nodules is decisive for the improvement of the patient's symptoms and thus for the success of the therapy, it was chosen as an objective follow-up parameter. [9, 17, 18]. Previous studies have shown that the greatest volume reduction occurs in the first 3 months after therapy [17]. Therefore, a follow-up period of 3 months was chosen in the study. Furthermore, it was investigated whether the amount of energy delivered per cubic volume of the nodule differed at regional and general anesthesia.

Treatment procedure and equipment

The nodules were treated with the EchoPulse device (Teraclion, Malakoff, France). The device consists of two ultrasound systems, a concave therapeutic head with 3 MHz and a diagnostic head with 7.5 – 12 MHz. The approximately 4 s long pulse produces heat by the absorption of acoustic energy and by converting it to thermal energy. The focal point is heated to 80 – 90 degrees Celsius and irreversible coagulation necrosis

Table 1 Baseline characteristics

	General anesthesia	Regional anesthesia
Number of patients	15	15
Average age of patients	50 years (range 26–73)	60 years (range 38–82)
Median nodule volume	6.65 ml (range 0.61–53 ml)	3.76 ml (range 0.8–7.76 ml)
Sex of patients		
Female	14	11
Male	1	4
Nodule morphology		
Solid	10	5
Complex	5	10
Indication for therapy		
Pressure symptoms	8	11
Autonomy	7	4

occurs, which is cleared by the immune system. The focal point is about 2 × 9 ml in size. A total of 10 s are required to heat 1 ml of the nodule [9–12].

The vessels supplying the nodule up to 3 mm are coagulated. The large vessels surrounding the nerves and vascular tracts remain intact and dissipate the heat generated. This is called a "heat sink" and protects vulnerable structures.

A cooling kit is installed before therapy. Nodal volume is measured by the Echopulse system. For regional anesthesia, 5 – 10 ml of Mecain 1% was applied subcutaneously to pericapsularly before therapy. General anesthesia was performed with Propofol. Initially, a dosage of approximately 1 mg/kgbw dependent on patient characteristics was given intravenously as a bolus over 1 – 5 min. Sedation was maintained with continuous administration at approximately 4.5 mg/kgbw/h dependent on patient characteristics.

The ultrasound probe is positioned on the hyperextended neck of the patient lying on his back. The device automatically creates a map of the tissue to be treated and the sensitive structures to be protected. The map is created by 10–20 sagittal and transverse layers, called voxels. The exact ablation zone of the nodule is determined by the treating doctor based on the voxel map. The device automatically selects a safety distance of 0.5 cm to the skin, 0.3 cm to the trachea and 0.2 cm to the carotid artery. In addition, the attending doctor monitors the therapy process with a diagnostic ultrasound head. Thus, the doctor can intervene manually and readjust the device at any time if he detects deviations or so-called heat bubbles which are an indicator for too high a temperature.

Statistical analysis

Because normal distribution of the data could not be assumed, statistical analysis was performed with nonparametric tests. Median pre-ablative volume reduction and median volume reduction of the total population and of both groups at three months were compared using the Wilcoxon signed-rank test. The difference in volume reduction at 3 months between the regional anesthesia group and the general anesthesia group was compared using the Mann–Whitney test. The amount of energy delivered per cubic volume of the nodule during regional and general anesthesia was compared using the Mann–Whitney test. The results were considered significant with $p < 0.05$.

Results

From 2014—2019, 30 patients (24 female and 6 male) were included in the study. Fifteen patients were treated in center 1 from 2014 to 2017, and 15 patients were treated in center 2 from 2016 to 2019. The average age of the patients was 55 years (26 to 82 years). Fifteen patients were treated with general anesthesia (0 in center 1 and 15 in center 2). Fifteen patients received regional anesthesia (15 in center 1 and 0 in center 2).

The median nodule volume before therapy was 4.2 ml (range 0.61–53 ml). In patients under general anesthesia, the median volume was 6.65 ml (range 0.61–53 ml). In patients under regional anesthesia, the median volume was 3.76 ml (range 0.8–7.76 ml).

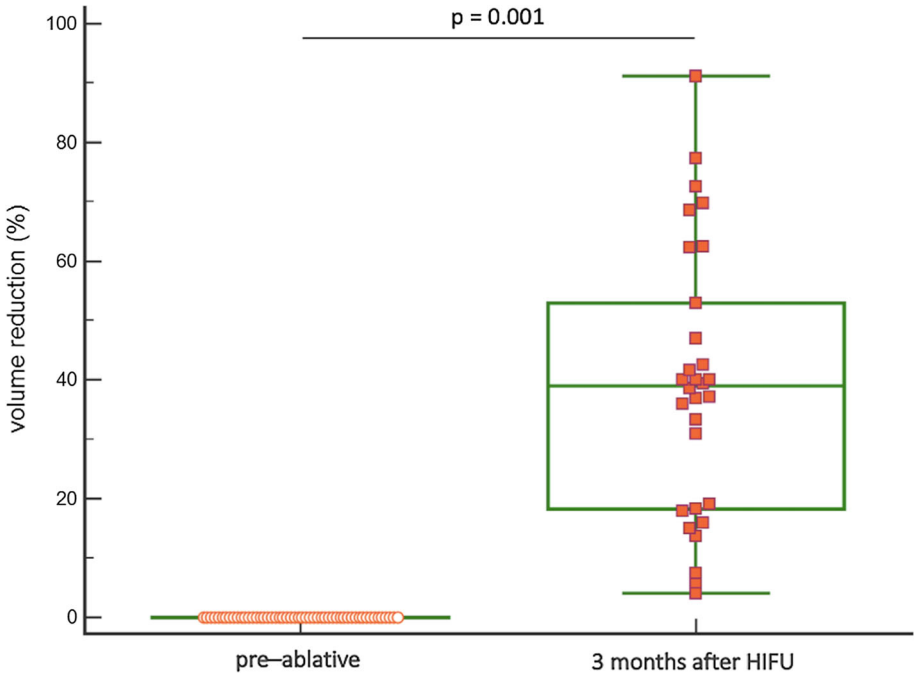

Fig. 1 Comparison of volume reduction of benign thyroid nodules before and three months after HIFU performed with the Wilcoxon signed-rank test. The total study population had an average volume reduction of 39.26% (range 4.03–91.16%, $p < 0.001$, $n = 30$) at three months follow-up

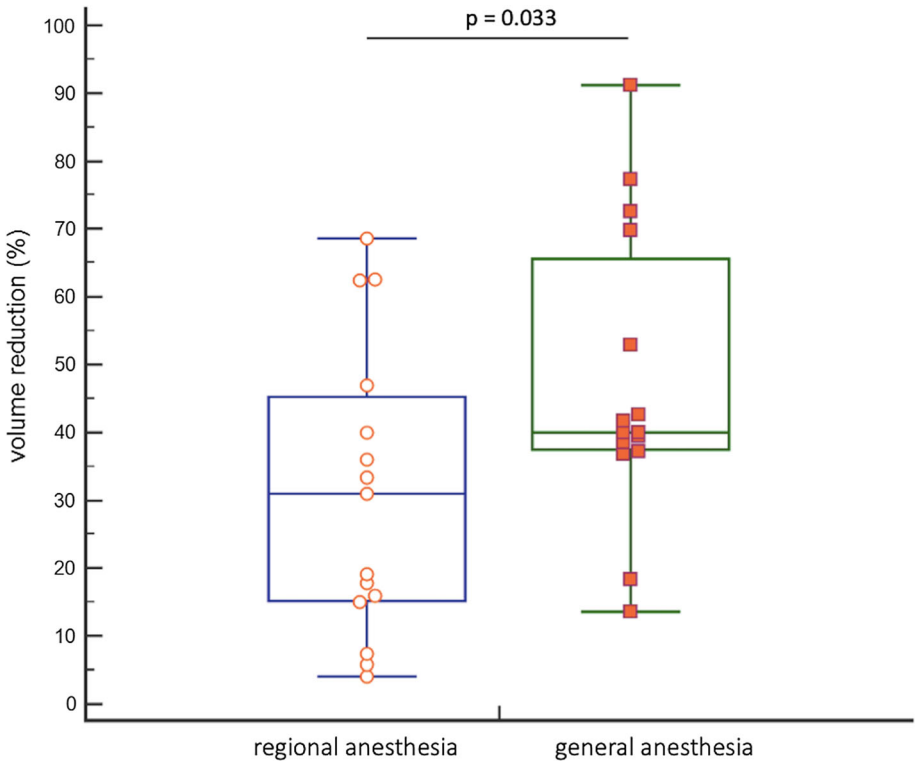

Fig. 2 Comparison of significant volume reduction of benign thyroid nodules 3 months after HIFU between regional and general anesthesia using the Mann–Whitney test. With $p = 0.033$, the volume reduction of the group treated under regional anesthesia was significantly higher

As shown in Fig. 1, the total study population had an average volume reduction of 39.26% (range 4.03–91.16%, $p < 0.001$, $n = 30$) at three months follow-up.

The group treated with regional anesthesia had an average volume reduction of 31.06% (range 4.03–68.63%, $p = 0.001$, $n = 15$) at three months follow-up. The group treated under general anesthesia had an average volume reduction of 47.46% (range 13.64—91.16%, $p = 0.001$, $n = 15$) at three months follow-up. Significant volume

reduction was found with $p < 0.05$ in the Wilcoxon signed-rank test in all three groups.

As shown in Fig. 2, the volume reduction after 3 months of the group treated under regional anesthesia was significantly different compared to the group treated under general anesthesia with $p = 0.033$ in the Mann–Whitney test.

Under regional anesthesia a median energy of 3,16 kJ/cm^3 (range: 0.96 – 8.2 kJ/cm^3) was delivered. Under general anesthesia, a median energy of 0.88 kJ/cm^3 (range: 0.18–1.63 kJ/cm^3) was delivered. The difference in energy delivery per cubic volume of the nodule in general and local anesthesia was significant with $p < 0.0001$ in the Mann–Whitney test.

The overall complication rate was 6.67%. No complications occurred in patients treated with regional anesthesia. Two patients treated with general anesthesia experienced reversible complications. Two patients suffered from recurrent laryngeal nerve paresis after therapy. In both patients, the vocal cords were freely movable again after 2 months with speech therapy. No patient suffered from an irreversible complication. The nodule sizes in these two patients were 6.65 ml and 11 ml, and the amount of energy delivered during therapy was 1.04 and 0.32 kJ/cm^3.

Discussion

The study showed that volume reduction in the group of patients treated under regional anesthesia differed significantly from the group of patients treated under general anesthesia. The average volume reduction was higher and less energy had to be delivered under general anesthesia than under regional anesthesia.

Different parameters during the intervention could explain why volume reduction was higher under general anesthesia despite less energy delivered during therapy.

During the therapeutic procedure, it is important to keep the focal point stable at the ablation zone. If the grid shifts due to movement, the device automatically stops the intervention and only partially treated lesions with a small ablation zone result. [19, 20] Due to the small ablation zone, it is very difficult to accurately target and heat the previous lesions again. If the patient is only locally anesthetized with regional anesthesia and moves, more incompletely heated lesions occur. Under general anesthesia, the patient does not move and therefore the intervention is less interrupted. Each ablation zone is heated completely. As a result, the volume reduction after therapy is greater in patients under general anesthesia and less energy is used due to the shorter treatment time. Research is already being conducted in relation to other organs to develop motion compensation techniques. [19–21]

The study indicates that in some cases, the intervention was interrupted and readjusted due to pain or deviations on the voxel map. However, no therapy was terminated early. Suboptimal placed regional anesthesia may have an impact on the patient's pain tolerance and thus on therapy tolerance. The longer heat is applied, the larger the ablation zone becomes. [12] If therapy is interrupted more frequently due to pain, more incompletely heated lesions result, and the ablation zone becomes smaller.

Whether the procedure can be performed under general anesthesia has to be evaluated individually for each patient. If regional anesthesia is chosen, it is important to minimize movements. It may be helpful to position the patient as comfortably as possible and to create a pleasant atmosphere so that the patient tolerates prolonged immobilization.

The group difference in pre-interventional nodal volume originates from the fact that, for large nodules, general anesthesia is more likely to be chosen than regional anesthesia. Since large nodules take longer to treat, the patient would not be able to lie still long enough under regional anesthesia.

More complications were observed in patients treated under general anesthesia. Recurrent laryngeal nerve paresis occurred but was reversible after speech therapy. Irreversible complications did not occur. The fact that more complications occurred under general anesthesia may be due to the patients' inability to provide feedback about pain or discomfort. With regional anesthesia, the patient can alert the doctor and the doctor can stop and readjust the procedure. Complications primarily involved the recurrent laryngeal nerve rather than the other vulnerable structures, such as the carotid artery and jugular vein. These structures, unlike the recurrent nerve, have a higher heat sink and are therefore better protected [12]. In the recurrent nerve, heat is not dissipated as well, causing it to be damaged more quickly. The complications occurred in large nodules, but not with greater amount of energy. Since the nodules were large nodules, it is likely that they were located near the nerve. Consideration should be given to neuromonitoring of the recurrent nerve under general anesthesia.

Other nodal characteristics that may have an impact on the therapeutic outcome of HIFU is nodal morphology [22, 23]. How nodal morphology affects volume reduction after HIFU has to be systematically investigated.

The advantage of HIFU over other thermoablative procedures is that it does not penetrate the skin. Therefore, there is no risk of infection and no scars are created. It does not require puncturing the thyroid capsule, and there is no risk of bleeding.

It was observed that patients complained of pain during therapy of superficial nodules with MWA and RFA. [8, 10]

In addition, HIFU can be used to treat small nodules more precisely due to the small focus (approximately 2 by 9 mm) and less surrounding tissue is damaged. The procedure is also better suited to be repeated several times, for example, in the case of large nodules.

Therefore, HIFU is an attractive alternative for benign thyroid nodules.

Conclusion

When comparing the types of anesthesia, the study showed that patients under general anesthesia had a higher volume reduction than patients under regional anesthesia. In addition, less energy was delivered under general anesthesia than under regional anesthesia. Therefore, after consideration of individual patient factors, general anesthesia is advantageous for HIFU of benign thyroid nodules. In the follow-up, it is particularly important to observe the recurrent laryngeal nerve.

Declarations

Conflict of interest The authors declare that they had no conflict of interest.

Ethical standards The study has been approved by the ethics committees and complies with the Declaration of Helsinki and local regulations.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Papini E, Monpeyssen H, Frasoldati A et al (2020) European thyroid association clinical practice guideline for the use of image-guided ablation in benign thyroid nodules. Eur Thyroid J 9:172–185
2. Happel C, Kranert WT, Bockisch B et al (2016) 131I and 99m Tc-uptake in focal thyroid autonomies development in Germany since the 1980s. Nuklearmedizin 55:236–241
3. Durante C, Grani G, Lamartina L et al (2018) The diagnosis and management of thyroid nodules. JAMA 319:914
4. Giovanella L, Avram AM, Iakovou I et al (2019) EANM practice guideline/SNMMI procedure standard for RAIU and thyroid scintigraphy. Eur J Nucl Med Mol Imaging 46:2514–2525
5. Lang BHH, Wu ALH (2017) High intensity focused ultrasound (HIFU) ablation of benign thyroid nodules - a systematic review. J Ther Ultrasound 5:11
6. Dietlein M, Grünwald F, Schmidt M et al (2016) Radioiodtherapie bei benignen Schilddrüsenerkrankungen (Version 5). Nuklearmedizin 55:213–220
7. Federführende Fachgesellschaft:Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) (2015) Operative Therapie benigner Schilddrüsenerkrankungen. AWMF online
8. Korkusuz H, Gröner D, Racynski N et al (2018) Thermal ablation of thyroid nodules: are radiofrequency ablation, microwave ablation and high intensity focused ultrasound equally safe and effective methods? Eur Radiol 28:929–935
9. Sennert M, Happel C, Korkusuz H et al (2018) Further investigation on high-intensity focused ultrasound (HIFU) treatment for thyroid nodules. Acad Radiol 2:88–94
10. Korkusuz H, Fehre N, Sennert M et al (2015) Volume reduction of benign thyroid nodules 3 months after a single treatment with high-intensity focused ultrasound (HIFU). J Ther Ultrasound 3:4
11. Korkusuz H, Sennert M, Fehre N et al (2015) Localized thyroid tissue ablation by high intensity focused ultrasound: volume reduction, effects on thyroid function and immune response. Fortschr Röntgenstr 187:1011–1015
12. Korkusuz H (2016) Thermoablation von Schilddrüsenknoten. Nuklearmediziner 39:227–231
13. Hill CR, Haar GR (1995) Review article: high intensity focused ultrasound–potential for cancer treatment. Br J Radiol 68:1296–1303
14. Wu F, Wang ZB, Cao YD et al (2003) A randomised clinical trial of high-intensity focused ultrasound ablation for the treatment of patients with localised breast cancer. Br J Cancer 89:2227–2233
15. Yang R, Sanghvi NT, Rescorla FJ et al (1993) Liver cancer ablation with extracorporeal high-intensity focused ultrasound. Eur Urol 23:17–22
16. Chung SR, Baek JH, Suh CH et al (2020) Efficacy and safety of high-intensity focused ultrasound (HIFU) for treating benign thyroid nodules: a systematic review and meta-analysis. SAGE J 61:1636–1643
17. Trimboli P, Pelloni F, Bini F et al (2019) High-intensity focused ultrasound (HIFU) for benign thyroid nodules: 2-year follow-up results. Endocrine 65:312–317
18. Prakash PS, Oh HB, Tan WB et al (2019) The efficacy and safety of high-intensity focused ultrasound (HIFU) therapy for benign thyroid nodules—a single center experience from Singapore. World J Surg 43:1957–1963. https://doi.org/10.1007/s00268-019-04976-2
19. Muller A, Petrusca L, Auboiroux V et al (2013) Management of respiratory motion in extracorporeal high-intensity focused ultrasound treatment in upper abdominal organs: current status and perspectives. Cardiovasc Intervent Radiol 36:1464–1476
20. Diodato A, Cafarelli A, Schiappacasse A et al (2018) Motion compensation with skin contact control for high intensity focused ultrasound surgery in moving organs. Phys Med Biol 63:035017
21. Bing C, Cheng B, Staruch R et al (2019) Breath-hold MR-HIFU hyperthermia: phantom and in vivo feasibility. Int J Hyperthermia 36:1083–1096
22. Haar G, Coussios C (2007) High intensity focused ultrasound: Physical principles and devices. Int J Hyperthermia 23:89–104
23. Izadifar Z, Izadifar Z, Chapman D et al (2020) An introduction to high intensity focused ultrasound: systematic review on principles, devices, and clinical applications. JCM 9:460