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Review

Current status and perspectives of ultrasound-guided ablation techniques in patients with primary hyperparathyroidism

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Abstract

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by elevated or inappropriately parathormone levels. The most common cause of PHPT is solitary parathyroid adenoma (80-85%). Parathyroid surgery generally encompasses symptomatic PHPT and asymptomatic patients who meet the surgical guideline criteria. If surgery is contraindicated, several non-surgical ablative techniques can be conducted to eliminate the pathological parathyroid tissue, which causes tissue necrosis in the affected gland. This review aims to look into the most recent studies on the efficacy of percutaneous ethanol injection therapy (PEIT), laser ablation (LA), radiofrequency ablation (RFA), microwave ablation (MWA), and high-intensity focused ultrasound (HIFU) in treatment of PHPT and analyze their application prospects. PEIT is a classic method that is less commonly used nowadays. The analysis of thermal ablation methods revealed that LA is inefficient and requires considerable repetition. Meanwhile, the MWA and RFA have a cure rate of over 85% and fewer complications; it seems that they have the potential to replace surgical methods in the future.

Keywords: Hyperparathyroidism, Primary hyperparathyroidism, Parathyroid adenoma, Ethanol ablation, Laser ablation, Radiofrequency ablation, Microwave ablation, High-intensity focused ultrasound

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Introduction

The typical parathyroid gland has a lentiform or ovoid shape and a yellowish-brown color. The four parathyroid glands are in pairs on either side of the midline. Superior parathyroid glands are usually located on the posterior surface of the thyroid gland, above the point at which the recurrent laryngeal nerve crosses the inferior thyroid artery (1). The inferior parathyroid glands are usually located below the inferior thyroid artery (Figure 1). The quantity and position of the parathyroid glands may vary significantly in individuals (2).

Parathyroid glands secrete parathormone, which regulates calcium and phosphorus metabolism in the body. An increase in parathyroid hormone (PTH) levels in the blood is known as hyperparathyroidism (4). It can be divided into primary hyperparathyroidism (PHPT), secondary hyperparathyroidism, tertiary hyperparathyroidism, and pseudohypoparathyroidism (5).

Primary hyperparathyroidism is an endocrine disorder characterized by elevated or inappropriately normal PTH levels and hypercalcemia in a patient with no prior history of renal disorder. As the third most common endocrine disorder, it affects 0.3% of the general population and 1%-3% of postmenopausal women. The incidence of PHPT varies according to the gender and ethnicity of individuals. A solitary parathyroid adenoma is the most common cause of PHPT (80-85%), followed by parathyroid hyperplasia (10-15%), multiple adenomas (5%), and parathyroid carcinoma (1%) (6). Clinical presentation of PHPT includes recurrent kidney stones, osteoporosis fibrosa cystica, hypercalcemic crisis, and neuromuscular dysfunction characterized by type II muscle cell atrophy. Among the classical symptoms, nephrolithiasis is the most common, occurring in 15%–20% of newly diagnosed patients (7).

PHPT also presents less specific symptoms, such as muscle weakness, mild cognitive disturbances, hypertension, left ventricular hypertrophy, and valvular calcification (8).

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Implication for health policy/practice/research/ medical education

Our review study shows that percutaneous ethanol injection therapy is a classic method for solitary parathyroid adenoma-induced primary hyperparathyroidism.

Asymptomatic patients can receive medical therapy for bone preservation, however this does not usually lead to long-term sustained control of hypercalcemia and requires lifelong monitoring (9).

The standard treatment for symptomatic PHPT is surgical excision of the parathyroid glands (10). It has been shown that the surgical method might not be suitable for elderly patients and/or patients with comorbidities due to technical difficulties and/or a high risk of anesthesia during surgery (11). If surgery is contraindicated, several non-surgical ablative techniques such as selective ultrasound-guided percutaneous ethanol injection therapy (PEIT) and ultrasound-guided thermal ablation such as laser ablation (LA), radiofrequency ablation (RFA), microwave ablation (MWA), and high-intensity focused ultrasound (HIFU) can be conducted to eliminate the pathological parathyroid tissue, which causes tissue necrosis in the affected gland(12). In most cases, ablative techniques are studied in animal studies, case reports, and small-scale clinical trials. To reach comprehensive and reliable conclusions, this review study aims to look into the most recent studies on the efficacy of PEIT, LA, RFA, MWA, and HIFU in treatment of PHPT and analyze their application prospects.

Search strategy

The studies were identified using the PubMed database, EMBASE, Scopus, and DOAJ and published until February 7, 2023. The search was performed using the following keywords; hyperparathyroidism, primary hyperparathyroidism, parathyroid adenoma, ethanol ablation, laser ablation, radiofrequency ablation, microwave ablation, and high-intensity focused ultrasound.

The clinical trials, systematic reviews, and retrospective and prospective studies were included. Three authors reviewed all study abstracts. We included studies that reported the efficacy of non-surgical techniques for treating PHPT. Studies written in languages other than English were excluded. All selected studies were qualitatively analyzed too.

Treatment methods

Eliminating the pathological parathyroid tissue is the purpose of PHPT treatment.

This can be accomplished through parathyroidectomy or ablative methods that results in pathological gland tissue necrosis (13).

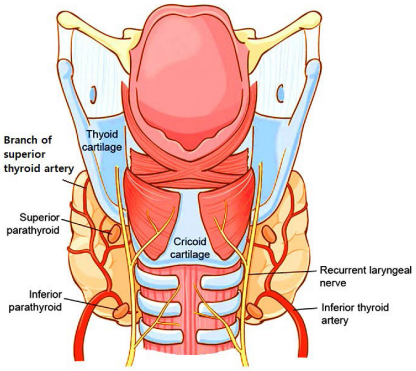

Figure 1. Parathyroid glands anatomy (3).

Surgical excision

Parathyroidectomy is the standard treatment for PHPT caused by a parathyroid adenoma due to its high long-term success rate. Surgery guidelines have specified this as the treatment of asymptomatic PHPT in patients with the following criteria (14):

1. Serum calcium >1.0 mg/dL above upper limit of normal
2. Bone marrow density by bone density scan (DXA); T score lower than – 2.5 at the lumbar spine, total hip, femoral neck, distal radius, or vertebral fracture.
3. Creatinine clearance less than 60 mL/min, or 24-hour urine calcium more than 400 mg/dL or presence of nephrolithiasis or nephrocalcinosis.
4. Age younger than 50 years.

During the past two decades, the surgical method has changed from bilateral neck exploration to unilateral exploration and finally to minimally invasive endoscopic procedures (15).

Bilateral cervical surgical exploration performed by a skilled and experienced parathyroid surgeon has a cure rate of 95-98% and a minimal risk of complications (12).

Radical neck explorations and general anesthesia complications may affect morbidity. It is even more significant in elderly patients or with a comorbid condition. As an extensive surgery, parathyroidectomy may not be the best choice for patients with a single parathyroid adenoma; young females may also be discouraged due to surgical scar formation (16). It might have some complications such as infection, hematoma, neck swelling, and long-term low serum calcium levels due to removal or damage to all of the parathyroid glands. The recurrence rate one year after surgery has been reported about 30% in previous studies (17). Various non-surgical ablative techniques can be used in cases with contraindications to surgery.

Non-surgical ablative techniques

Percutaneous ethanol injection therapy

As a sclerosant, ethanol causes the necrosis of tumor tissue and thrombosis of small blood vessels. Before starting

ablative therapy, it is necessary to accurately identify the pathological parathyroid tissue via ultrasonography (18). In this method, 3-5 ml of 96% ethanol or the equivalent volume of half of the affected glands can be administered in two or three sessions, separated by 24 hours (19). Serum calcium and PTH levels usually return to the normal range, 36-120 hours and 6-78 hours after the procedure, respectively. In a five-year follow-up, approximately 65 percent of patients maintained normal serum calcium and PTH levels after ethanol administration (12).

A historical perspective

Solbiati et al in 1985 developed ultrasound-guided selective PEIT in Italy to manage parathyroid hyperplasia without parathyroidectomy. In most cases, this method was used to treat secondary or tertiary hyperparathyroidism, depending on the severity of the problem (20). Later in 1987, The Mayo Clinic reported the successful treatment of persistent PHPT by the PEIT method (21). From 1988 to 1996, Cercueil et al evaluated the long-term results of ultrasound-guided PEIT for treating parathyroid adenoma in 27 patients. In 2 years of follow-ups, 58% recovery was reported. Even though Temporary recurrent laryngeal nerve damage and hypocalcemia occurred in some patients, no long-term complications were reported (22). In another study in 1988, Vergès et al investigated 31 inoperable patients using ultrasound-guided percutaneous ethanol injection into the adenoma. Plasma calcium and PTH levels were measured 48 hours after PEIT and several times during the subsequent 5-year follow-up. They reported that percutaneous ethanol injections under ultrasound guidance were effective in 64% of the cases of hyperparathyroidism, suggesting that this method can be quite beneficial in patients at high surgical risk. Although this treatment was well tolerated and had no significant side effects and an accurate ultrasound, location of the adenoma is required (23).

Current studies

Stratigis et al conducted a prospective study in 2008 to evaluate PEIT as an alternative to surgery for patients with PHPT. About19 patients with high-risk PHPT for surgery were included in this study. To normalize PTH levels, ethanol (95%) was injected into the parathyroid glands under ultrasonic guidance. During the 6-month follow-up period, 58% of patients responded to this treatment. They concluded that PEIT is a safe and effective non-surgical treatment option for patients with PHPT who cannot undergo surgical treatment (24).

According to some reports, ultrasound-guided PEIT was used to treat patients with solitary parathyroid adenoma after drug therapy failed (25).

Ultrasound-guided RFA and PEIT were combined in 2017 by Shenoy et al, for better control of hypercalcemia and PTH levels in PHPT due to parathyroid adenoma. As evidenced by the normalization of PTH levels and the improvement in symptoms at a 2-year follow-up, PEIT and RFA sequentially can be considered effective short-term options in surgically complex cases, contributing to long-term recovery as well (26).

Meanwhile, Yazdani et al evaluated ultrasound-guided PEIT in 2020 for treating parathyroid adenomas. An experienced interventional radiologist performed this procedure under real-time ultrasound guidance on 39 PHP patients with parathyroid adenoma who were not candidates for surgery. During 1-year follow-up, 85% of patients improved after PEIT. The results of this study have demonstrated that ultrasound-guided PEIT is an effective alternative treatment option for PHPT patients who are not candidates for surgery or general anesthesia. Further, it has not been associated with significant complications if administered by an experienced interventional radiologist (27).

Based on the published data, PEIT appears to be associated with only a few side effects, such as peri-glandular fibrosis, hypocalcemia, recurrent laryngeal nerve injury, and incomplete necrosis of the adenoma (28). Despite reports of high recurrence of HPT, ultrasound-guided PEIT effectively controlled parathyroid adenoma and consequence in quality of life improvement (27,28).

Thermal ablation

Laser ablation

A laser is a concentrated light ray. Following the insertion of an optical fiber inside the tissue, the photons released by the laser source focus the heat on tip of the fiber. The temperature in the area can instantly rise to 100 degrees Celsius to accomplish the therapeutic goal of coagulation and necrosis of local tissue (29,30). LA prevents consequences like fibrosis and adhesion by creating a distinct demarcation line between laser-treated necrotic tissue and unaffected surrounding tissues (29). Lasers can split energy across multiple thin, flexible fibers, which are particularly easy to use (31); therefore, laser probes may cause less damage and consequently have greater cosmetic potential than other types of thermal ablation (32).

Appelbaum et al performed LA as a therapeutic method for functional parathyroid adenomas in 12 patients. HPT symptoms and serum levels of parathormone and calcium resolved after 6 months and showed a significant, sustained response during a 2-year clinical follow-up (32).

In other studies, conducted in this field, it was observed that the PTH level decreased only slightly and transiently (33). There have been two theories to explain this condition; the ability of parathyroid cells to proliferate after LA and the small number of adenomatous cells that remain after the procedure (34). To prevent marginal regrowth, complete resection of the border of the parathyroid nodule is essential (29). However, to completely recover from PHPT, some patients require surgery. Therefore, it indicates that LA is not effective as a long-term treatment of PHPT (35). LA therapy did not

cause long-lasting side effects. Transient dysphonia is the most common complication reported in patient follow-ups (33).

Radiofrequency ablation

Radiofrequency ablation is an electromagnetic energy source that induces coagulation an electrode with high-frequency alternating current (3 kHz to 300 GHz) to cause thermal injury and coagulative necrosis in soft tissue (36) (Figure 2). RFA is often applied to nodules with a diameter of less than 15 mm but is less effective for larger nodules with rich blood flow (37). Li et al treated 25 patients with PHPT using RFA, serum PTH and calcium levels normalized in 84% (21/25) of the patients. One year after RFA, hyperplastic glands volume decreased by greater than 70%, and just 20% (5/25) of the patients experienced mild complications (four cases of mild pain and one case of temporary hypocalcemia) (38).

There are limited data regarding the complications of parathyroid adenoma ablation; however, hypocalcemia and voice hoarseness has been reported in some cases (39).

Microwave ablation

Microwave ablation operates with electromagnetic waves within the radiofrequency spectrum; as a result, it is a subgroup of RFA, but its heating mechanism is different. Magnetrons are used in the MWA generator to generate microwaves, transmitted by coaxial cable and ablation antenna to the ablation area. Through high-frequency vibration, polar molecules (mostly water molecules) generate heat and rapidly rising temperature to 150 degrees Celsius results in cell dehydration necrosis (40). The MWA advantages include rapid temperature rise, high heat, short treatment period, extensive ablation range, and total inactivation of tumor tissue (41).

Previously, Zhang et al perform MWA for PHPT treatment in 35 cases with six months follow-up. They concluded that MWA could significantly reduce serum PTH, calcium, and phosphorus levels; it was also relatively safe and long lasting in treating PHPT patients (41).

In another study, Liu et al perform a comparison between MWA and parathyroidectomy for PHPT in 56 cases with similar basic characteristics. There was a significant decrease in operation time and blood loss in the MWA group compared to the surgical group ($P<0.01$). After six months, 82.1% of patients treated with MWA had normal PTH and serum calcium levels; their study showed that the cure rate and prevalence of complications were not different between the two groups (11).

In another study, Fan et al treated 22 patients with MWA for PHPT. In a one-year follow-up, serum PTH and calcium levels normalized in 19 cases (86.36%), and nodules disappeared completely in 15 cases (68.2%). They suggest that MWA is an effective method for managing PHPT (42).

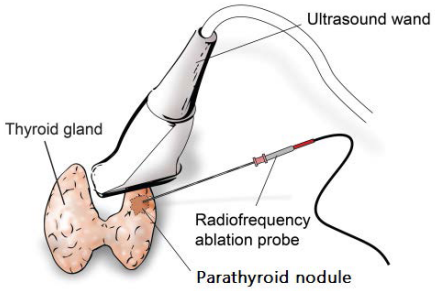

Figure 2. Schematic diagram of RFA in treatment of PHPT.

High-intensity focused ultrasound

High-intensity focused ultrasound is three-dimensional conformal therapy. An external mechanical motion under ultrasonic monitoring can disrupt the focus from the ablation area (43) (Figure 3). As high-intensity ultrasound passes through tissues, the tissue constantly absorbs the energy and converts it to heat. The tissue temperature rises rapidly in the focal area to 65–100°C, resulting in cells necrosis. Despite a successful application to prostate tumors and uterine fibroids, the clinical experience in managing parathyroid adenoma is limited(44).

According to a study by Kovatcheva et al in 2014, HIFU effectively treated 13 patients with parathyroid adenomas. Patients significantly decreased PTH and serum calcium levels; subcutaneous edema and vocal cord damage were reported in a few patients after the procedure. The power disintegrated by HIFU has correlation with the cure rate, not the damage of the vocal cords which is primarily associated with the depth of adenoma (45).

In a similar study, HIFU was performed on four patients by Ambrosini et al They reported mild discomfort and transient hoarseness following HIFU (46).

Percutaneous ethanol injection therapy versus thermal ablation

Since PEIT has a high recurrence rate, the necessity of repeating procedures, and having more side effects than thermal ablation, it's no longer the best choice for PHPT

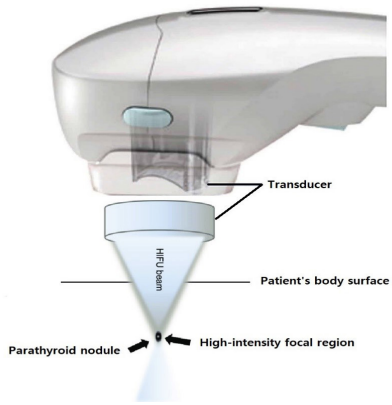

Figure 3. Scheme of HIFU in the treatment of PHPT.

treatment (47).

On the other hand, thermal ablation has significantly decreased PTH and calcium levels three to six months after the procedure and its most common complication was self-limited transient dysphonia without substantial disabilities (48).

Radiofrequency ablation versus microwave ablation

Ablation techniques vary considerably in their fundamental mechanisms. Microwave and RFA are widely used and innovative improvements in thermal ablation technologies (49). MWA employs an electromagnetic area surrounding an insulated and electrically independent antenna, whereas RFA uses current flow through conducting electrodes inside the body (50). The ablation zone, treatment time, and therapy sessions may differ between the two modalities (51). The high core temperature (RFA versus MWA; 110°C versus 150°C) can carbonize the ablation zone and reduce absorption. However, MWA minimizes this phenomenon by low-energy, brief radiation period, and multiple-spot ablation procedure(52).

These devices have several advantages for treating PHPT, including minimal invasiveness, high tolerance, and repeatability, as well as preventing overheating and maximizing energy efficiency (39,51).

Clinical outcomes showed that the efficacy of these methods does not differ significantly (MWA: 88.3%, RFA: 88.9%) (53). In both MWA and RFA, the small diameter (less than 7 mm) of the adenoma nodule is a specific risk factor for failing the ablation treatment (53). There was no significant difference in side effects between the RFA and MWA groups. The most common complication following ablation was transient hoarseness (5%) (52). Compared to surgical resections with a cure rate of 95%, MWA and RFA have slightly lower cure rates (88%) (12,53).

Conclusion

Our study shows PEIT is a classic method that is less commonly used nowadays because of its low recovery rate. The analysis of thermal ablation methods revealed that LA is inefficient and requires considerable repetition. Further studies are needed to reach a comprehensive conclusion about the efficacy of the HIFU technique. Meanwhile, The MWA and RFA have a cure rate of over 85% and fewer complications; it seems that they have the potential to replace surgical methods in the future, especially in patients who are not candidates for surgery.

Authors' contribution

Conceptualization: MJ, PY.
Validation: AB.
Investigation: ARK, MJ, PY.
Resources: AB.
Data curation: ARK, MJ, PY.
Writing-original draft preparation: ARK, MJ, PY.
Writing-reviewing and editing: ARK, AK, DR.
Visualization: MJ, MS.
Supervision: AB.
Project management: AB.

Conflicts of interest

The authors declare no conflict of interest related to the subject matter or materials discussed in this article.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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