Microwave ablation of hyperplastic parathyroid glands is a treatment option for end-stage renal disease patients ineligible for surgical resection

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ABSTRACT

Background: Secondary hyperparathyroidism (SHPT) is a frequently encountered problem in patients with end-stage renal disease (ESRD). Some patients with severe SHPT could not be managed by medical treatment and are ineligible for surgical resection.

Purpose: Our objective was to evaluate the efficacy, safety of microwave ablation (MWA) on these patients.

Materials and Methods: Between 1 April 2015 and 28 February 2017, 35 patients (M/F 19/16, age 49.8 ± 12.9 years) were enrolled. All patients were treated with MWA. Levels of intact parathyroid hormone (iPTH) and of serum calcium and phosphorus were compared pre- and post-ablation. Repeated-measures ANOVA was used to compare treatment outcomes pre- and post-ablation.

Results: Complete ablation was achieved in all 63 glands in the 35 patients with SHPT. The mean follow-up time was 15.9 ± 2.2 months. The maximum gland diameter was 6–31 mm (mean, 14.9 ± 5.5 mm). The trends of the changes in iPTH and calcium levels showed a curve: the level of iPTH and calcium at the end of follow up was not significantly lower than pre-ablation (p = .462). The trend in the change in phosphate levels showed a straight line; the level of phosphate at 6 months post-ablation and at the end of follow up both were significantly lower than pre-MWA (p < .001). There was no major complication.

Conclusions: In this series, MWA was used successfully to treat SHPT patients who are ineligible for surgical resection.

Introduction

Secondary hyperparathyroidism (SHPT) refers to excessive secretion of parathyroid hormone (PTH) by the parathyroid glands in response to hypocalcemia and associated hyperplasia of the glands. This disorder is seen especially in patients with end-stage renal disease (ESRD) [1,2]. Its serious clinical complications include renal osteodystrophy, neurotoxicity and vascular calcification. The condition has a high impact on fractures and mortality in ESRD patients [3,4]. The majority of patients with SHPT can be managed by medical treatment, such as phosphate binders [5,6], orally active vitamin D sterols [7,8], intravenous vitamin D analogs [9,10] and cinacalcet [11,12]. However, medical treatment does not always result in control of parathyroid disorders. Parathyroidectomy is recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for patients with chronic kidney disease-related mineral and bone disorders [13]. Parathyroidectomy is recommended in patients with severe hyperparathyroidism (persistent serum levels of intact PTH >800 pg/mL or 88.0 pmol/L) associated with hypercalcemia and/or hyperphosphatemia refractory to medical therapy. Parathyroidectomy can induce a marked improvement in SHPT: postoperative serum phosphorus and calcium levels are maintained readily within their target ranges, and quality of life and survival rates are improved. However, some patients are ineligible for surgical resection, such as those who are not suitable for highly invasive surgery under general anaesthesia, those whose parathyroid glands are located in an area that renders resection difficult, those in whom it is difficult to resect all affected parathyroid tissues, and those with recurrent SHPT (iPTH level >300 pg/mL within 6 months postoperatively, which then increased again >6 months postoperatively [14,15]), and those who have undergone surgery at least once before. Treatment would be a challenge for these patients and their clinicians. Unfortunately, little research has been reported regarding treatment recommendations for these patients at present. Based on our preliminary experience, microwave ablation (MWA) is safe and...
effective for destroying parathyroid gland tissue in patients with ESRD [15,16]. In this study, we report new data in terms of safety and efficacy at mid-term of parathyroid MWA in SHPT patients ineligible for surgical resection.

Materials and methods

Patients

The study protocol was approved by the Human Ethics Review Committee of the China-Japan Friendship Hospital. Written informed consent was obtained from each patient before MWA.

Of 249 patients with severe SHPT seen in the nephrology department between 1 April 2015 and 28 February 2017, 35 who were ineligible for surgical resection met the inclusion criteria for MWA. The inclusion criteria were (1) ESRD with SHPT and medical intolerance (uncontrolled SHPT despite adequate medical therapy), (2) iPTH level $\geq 600$ pg/mL [1], (3) at least one enlarged parathyroid gland (maximum diameter of gland $\geq 6$ mm) accessible to MWA, (4) increased $^{99}$mTc sestamibi (MIBI) accumulation in the gland during both the early and delayed phases, (5) ineligible for surgical resection (such as patients who have undergone renal transplantation, coronary artery bypass surgery, cardiac valve replacement or coronary stent implantation; patients with thoracic deformities; patients whose parathyroid glands were located in a difficult-to-resect area (such as parathyroid glands located within the mediastinum, thymus or thyroid, as well as the tracheoesophageal groove, retroesophageal region and submandibular region), patients in whom it would be difficult to resect all affected parathyroid tissues, and patients with recurrent SHPT who have undergone one or more previous surgeries), (6) prothrombin time $\leq 25$ s, activated partial thromboplastin time $\leq 45$ s, and platelet count $\geq 100 \times 10^9$/L and (7) no intractable complication (such as cardiac insufficiency or hypertension that could not be controlled by drugs).

Exclusion criteria were (1) iPTH level $< 600$ pg/mL, (2) medication effectiveness (SHPT controlled with adequate medical therapy), (3) ultrasound examination showing no hyperplastic parathyroid glands, (4) MIBI scan of the gland without radionuclide accumulation, (5) candidate for parathyroidectomy, (6) abnormal coagulation function tests (such as prothrombin time $> 25$ s, activated partial thromboplastin time $> 45$ s, and platelet count $< 100 \times 10^9$/L) and (7) intractable complication (such as cardiac insufficiency or hypertension that could not be controlled by drugs).

Percutaneous MWA procedure

MWA was performed by an experienced radiologist. The ultrasound characteristics of the affected parathyroid glands (echo features on ultrasound, maximum diameter and position) were evaluated. A microwave generator and 17-gauge internally cooled antenna with a 0.4 cm tip (Intelligent Basic Type Microwave Tumor Ablation System, Nanjing ECO Microwave System, Nanjing, China) were used for the ablation procedures. The antenna was inserted freehand into the parathyroid gland to ablate one-by-one under US guidance (Apio 500, Toshiba Medical Systems). The detailed ablation procedures have been described previously [16]. After ablation, a contrast-enhanced ultrasound (CEUS; SonoVue; Bracco, Italy) was performed to evaluate the extent of ablation of the parathyroid gland [17]. The ablation was considered complete if the non-enhanced zone on CEUS covered the ablated gland. An additional ablation was performed immediately if there was nodular enhancement within a gland.

An anesthesiologist was present to assist the radiologist in cases of anesthesia, pain, vasovagal reactions or potentially uncontrollable hematoma pressing on the trachea during the procedure.

Mild compression was applied to the site of the needle insertion for 20 min and patients remained under observation for 2 h after the procedure.

Clinical data collection and follow-up

Clinical data were collected for all patients, including the iPTH, serum calcium and serum phosphate levels, before and 6 months after ablation and at the end of follow-up (cut-off 30 September 2017). All data were obtained in the same laboratory at the China-Japan Friendship Hospital. Ultrasound was performed and evaluated at each follow-up evaluation post-ablation (6 months after ablation and at the end of follow-up) to identify complications and recurrence (the parameters, such as size (maximum diameter), volume and echogenicity (homogeneous or heterogeneous) of parathyroid gland were used for evaluation, CEUS also was performed.). Major and minor complications were defined according to the criteria of the Society of Interventional Radiology [18,19].

Definition of local recurrence and new occurrence

Local recurrence implied the appearance of a new parathyroid gland at the ablative margin after local eradication of all gland cells by ablation [20]. A new occurrence was a new parathyroid gland growing at another site.

Statistical analysis

Statistical analyses were performed using the JMP software (ver. 11.0; SAS, Institute Inc., Cary, NC). Continuous data were presented as means $\pm$ SD (normally distributed data) or medians and interquartile ranges (IQR, non-normally distributed data). Repeated-measures ANOVA was used to compare treatment outcomes pre- and post-ablation. Values of $p < .05$ were considered to indicate statistical significance.
underweight (weight implantation (area (recurrent SHPT with a history of one or more surgeries (mean 14.9 ± 5.5 mm). Reasons for ineligibility for surgery were four glands. The maximum gland diameters were 6.00–2.75 mmol/L). Of the patients, 18 had one hyperplastic parathyroid gland, 8 had two, 7 had three and 2 had four glands. The maximum gland diameters were 6–31 mm (mean 14.9 ± 5.5 mm). Reasons for ineligibility for surgery were recurrent SHPT (underwent one or more surgeries) 12, poor heart or lung function 10, renal transplantation 4, parathyroid glands located in a difficult-to-resect area 3, thoracic deformity 3, coronary stent implantation 1, advanced age (≥80 years old) 1 and underweight (weight = 24 kg; BMI = 12.2 kg/m²) 1.

**Technical outcomes after MWA**

All 63 glands in 35 patients were treated by MWA in a single treatment session. All 63 glands showed hyperenhancement in the arterial phase and were isoechic in the late phase on pre-ablation CEUS. This enhancement behavior was consistent with high parathyroid function. After ablation, all glands showed non-enhancement on CEUS, indicating complete ablation. Figure 1 shows a percutaneous MWA procedure. The maximum gland diameters were 6–31 mm (mean, 14.9 ± 5.5 mm) in these patients, whereas the size of the adenoma showed marked regression during the 6 months following ablation (3–25 mm, mean 10.8 ± 4.9 mm) and at the end of follow-up (0–23 mm, mean 7.7 ± 5.0 mm). At the end of follow-up, the local recurrence rate was 8.8% (3/34) and the new occurrence rate was 11.8% (4/34).

**Laboratory analyses**

As of 30 September 2017, the mean follow-up time was 15.9 ± 2.2 months. The trends of the changes in iPTH and calcium levels showed a curve, the level of iPTH and calcium at 6 months post-ablation were lower than those pre-ablation (both p < .0001), after then, iPTH remained relatively stable and the end of follow up, with no rebound (p < .0001), but calcium at the end of follow up was not significantly lower than pre-ablation (p = .462). The trend in the change in phosphate levels showed a straight line; the level of phosphate at 6 months post-ablation and end of follow up were both significantly lower than pre-MWA (p < .001, Table 2).

**Survival following MWA**

Nobody died during the 30-day post-MWA period. One died from cardiovascular diseases by the end of the follow-up (mean 15.9 ± 2.2 months). The mortality rate was thus 3.0% (1/33), and the survival rate was 97.0% (32/33) in these patients at the end of follow-up.

**Complications**

Complications related to MWA at our institution occurred in 28.6% of 35 patients, and no one was considered major. Minor complications included mild subcutaneous oedema in three patients, which resolved 2–4 days after MWA, prolonged vocal cord mobility impairment in two patients,
which improved within 2–3 months after MWA, and slight bucking (mild cough) on swallowing water in five patients, all recovering within 3 days to 2 months after MWA. All ablation-related minor complications showed spontaneous remission with no medical intervention. However, no other complication was reported during follow-up.

Discussion

Although parathyroidectomy has potential complications, such as transient or permanent hypocalcemia and laryngeal nerve injury, patients with SHPT can gain many benefits from surgery. These may include improved serum phosphorus and calcium levels, bone mineral density, survival and alleviation of symptoms. Thus, parathyroidectomy is currently recommended in the KDIGO for severe SHPT patients who fail to respond to medical therapy [13]. However, not all severe SHPT patients can be treated by parathyroidectomy. Some patients are not suitable for surgery for various reasons. Thus, such a treatment would be a challenge for these patients and their clinicians. There is currently no guideline or recommendation for these patients as to what to do next. Fortunately, there have

Figure 1. A 47-years-old female patient with a recurrent and ectopic SHPT nodule 2 years after parathyroidectomy was treated by microwave ablation (MWA). (A) A hypoechoic SHPT nodule (long thin arrow) closing to the right sympathetic nerve (short thin arrow) was disclosed to locate between the right carotid artery (long thick arrow) and jugular vein (short thick arrow) in ultrasound. (B) The CT scan showed that the SHPT nodule (long thin arrow) is between the right carotid artery (long thick arrow) and jugular vein (short thick arrow). (C) The SHPT nodule has radioactivity concentration (black arrow) in the late phase on MIBI scan. (D) A uniform hyperenhancement of the SHPT nodule (long thin arrow) between the right carotid artery (long thick arrow) and jugular vein (short thick arrow) was displayed in CEUS preablation. (E) The spacer fluid (white triangle) was injected around the right sympathetic nerve (short thin arrow) behind the right carotid artery (long thick arrow), jugular vein (short thick arrow) and SHPT nodule (long thin arrow) for preventing the nerve from thermal injury during ablation. (F) The hyperechoic signal emerging along the tip of antenna (white triangle) inside the SHPT nodule (long thin arrow) during ablation. (G) A non-enhancement area covered the SHPT nodule (long thin arrow) beside the jugular vein (short thick arrow) after MWA, suggesting complete ablation was achieved by MWA. (H) The SHPT nodule (long thin arrow) in front of right carotid artery (long thick arrow), jugular vein (short thick arrow) and sympathetic nerve (short thin arrow) was obviously shrinking 6 months after MWA in ultrasound.

Table 2. Laboratory data of SHPT patients before and after MWA.

|                     | Pre-ablation (n = 35) | Post-ablation (6 months) (n = 35) | End of follow-up (n = 33) |
|---------------------|----------------------|----------------------------------|--------------------------|
| iPTH (pg/mL)        | 1095.2 (845.0–1611.7)| 150.0 (66.7–251.0)*              | 270 (92.0–625.0)*        |
| Calcium (mmol/L)    | 2.53 (2.41–2.61)     | 2.17 (1.91–2.33)*                | 2.24 (2.13–2.47)         |
| Phosphorus (mmol/L) | 1.80 (1.36–2.41)     | 1.34 (0.85–2.44)*                | 1.68 (1.15–1.85)*        |

End of follow-up (cut-off on 30 September 2017): mean follow-up time was 15.9 ± 2.2 months. One patient died of cardiovascular disease by the end of follow-up, and the other one patient was lost to follow-up. Values are medians (IQR) for all variables.

* p < .01, vs. pre-ablation.
been many good studies on non-surgical treatments for hyperparathyroidism in recent years. Several case reports and case series have been published. Percutaneous injection of ethanol [21,22], acetate acid [23] and calcitriol [24] and thermal ablation, including radiofrequency (RF) [25,26], laser [27] and high-intensity focussed ultrasound (HIFU) [28,29], have been assessed in patients with hyperparathyroidism. A preliminary study by our group also confirmed that ultrasound-guided MWA was safe and effective in destroying parathyroid gland tissue in patients with SHPT [15,16]. At the same time others have done the same job [30,31].

MWA is an energy-based ablation technique; it creates a uniform electromagnetic field surrounding the antenna, causing rapid volume tissue heating via the oscillation of polar water molecules. However, chemical ablation (injection of ethanol, acetate acid or calcitriol) has the risk of solute leakage into the surrounding tissue, which could be harmful [32]. The incidence of injection-related complications with chemical ablation, such as hemorrhage, recurrent laryngeal nerve palsy caused by ethanol leakage, and adhesions to surrounding tissue, increases with the number of injections[32,33]. Our previous and other researcher's studies [16,34,35] also mentioned that MWA devices could create a uniform electromagnetic field surrounding the antenna. By the oscillation of polar water molecules, it can make volume tissue rapidly heating. Because MWA does not rely on the conduction of an electrical current, tissues temperatures can increase markedly. Compared with other ablation techniques (such as RF, laser and HIFU), MWA may translate into larger, faster and more consistent ablation zones. Thus, MWA maybe is more suitable for SHPT patients who are ineligible for surgical resection.

Because of high surgical or anesthetic risk, such as after renal transplantation, thoracic deformity, parathyroid glands in ectopic locations, advanced age, underweight and recurrent SHPT, these patients are not suitable for parathyroidectomy. First, regarding the treatment effect, we show a marked improvement in SHPT patients. A marked decrease in serum iPTH levels were observed post-ablation, and serum calcium and phosphorus levels also improved. At 6 months post-ablation and at the end of follow-up, neck US revealed complete ablation or almost 50% reduction in the size of the treated parathyroid lesions, compared with the size pre-ablation in all patients. Thus, ultrasound-guided MWA can be used effectively for SHPT treatment.

In clinical applications of parathyroid MWA, we have improved the technology, including (1) Before ablation, injection more spacer fluid than those in previous study (Normal saline: 40–60ml vs 20ml) surrounding SHPT nodule to fully separate the SHPT nodule from vital structure; (2) Provoking the SHPT nodule away from important structure like recurrent laryngeal nerve, carotid artery during ablation to avoid thermal damage. So, the incidence of complications has decreased significantly compared to our preliminary study [16]. In this study, MWA caused little trauma and few severe complications. There were no severe complications during ablation or the follow-up period. This suggests that ultrasound-guided percutaneous MWA is safe for ESRD patients.

According to literature reports, the recurrent and persistent hyperparathyroidism rates after parathyroidectomy were 0.83–26% and 0.4–15% [36–39], respectively. In our study, despite the poor physical conditions of and difficulties in managing these patients, the local recurrence rate was 8.8% (3/34) and the new occurrence rate 11.8% (4/34). Certainly, ablation differed from surgical treatment, but the long-term efficacy of MWA was not inferior to that of parathyroidectomy. Moreover, compared with other studies (the survival rate after parathyroidectomy was 90.4–97.1% at 1 year [40–42], and the 30-day postoperative mortality rate following parathyroidectomy was 3.1% [43]), the survival rate (97.0%) and the 30-day post-ablation mortality rate (0%) following MWA were not worse in our study. Despite the incidence of complications in this study was 28.6%, they were all spontaneous remission, with no medical intervention, including mild subcutaneous edema, prolonged vocal cord mobility impairment and slight bucking (mild cough) on swallowing water. There was no incidence of temporary or permanent recurrent laryngeal nerve palsy with and no incidence of wound hematoma or infection. Meanwhile, whether conventional parathyroid surgery or minimally invasive parathyroidectomy (MIP), the incidence of surgical severe complications was 1.1–3.1% [44–47], including wound hemorrhage or hematoma, recurrent nerve injury and so on. Moreover, the hospital stay was 1–3 days in our population. This suggests that MWA has many advantages such as fewer risks, faster recovery and fewer side effects compared with surgical treatment.

There are several limitations to this study. First, MIBI was not repeated after treatment to confirm the reduction/disappearance of activity. Second, longer-term follow-up is needed after MWA.

In a preliminary study [16], we have confirmed that MWA was safe and effective for destroying parathyroid gland tissue in patients with ESRD. In this study, we applied MWA to treat SHPT patients who are ineligible for surgical resection. In these patients, MWA is equally safe and effective, and there is no increase in complications due to prolonged follow-up. So, our study provides a new option for SHPT patients who are ineligible for surgical resection.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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