Microwave ablation versus parathyroidectomy for severe secondary hyperparathyroidism in patients on hemodialysis: a retrospective multicenter study

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ABSTRACT

Background: Microwave ablation is effective for severe secondary hyperparathyroidism, but the difference in efficacy between microwave ablation and parathyroidectomy remains unclear. In this multicenter retrospective cohort study, we compared the long-term clinical efficacy of microwave ablation and parathyroidectomy for severe secondary hyperparathyroidism undergoing hemodialysis.

Materials and methods: The patients were divided into microwave ablation and parathyroidectomy groups. The primary endpoint was the proportion of patients with intact parathyroid hormone (iPTH) concentrations within the target range (100–600 pg/mL) during the efficacy assessment phase. The secondary endpoints were (i) differences in iPTH concentrations over time between the two groups, and (ii) decreases in iPTH concentrations over time in the two groups.

Results: Microwave ablation was performed in 47/92 patients and parathyroidectomy in 45/92. Primary endpoint: iPTH concentrations within the target range were achieved during the efficacy assessment phase in 26/47 patients (55.3%) and in 14/45 (31.1%) patients in the microwave ablation and parathyroidectomy groups, respectively (p < .02). Secondary endpoints: (i) Mean iPTH concentrations during the efficacy assessment phase were significantly higher in the microwave ablation versus parathyroidectomy groups (649 ± 519 pg/mL versus 136 ± 228 pg/mL, respectively; p < .01). (ii) Mean decrease in iPTH concentration from baseline was 725 ± 605 pg/mL versus 1369 ± 478 pg/mL in the MWA versus parathyroidectomy groups, respectively (p < .01).

Conclusions: Ultrasound-guided percutaneous microwave ablation provides higher iPTH target-achieving rates than parathyroidectomy in patients with severe secondary hyperparathyroidism undergoing hemodialysis.

Introduction

Chronic kidney disease, a worldwide public health problem, is increasing in incidence and prevalence. The condition gradually develops into end-stage renal disease, necessitating renal replacement therapy in the form of hemodialysis, peritoneal dialysis, or kidney transplantation. Secondary hyperparathyroidism is a common complication of chronic kidney disease and end-stage renal disease [1,2]. The condition is characterized by disturbances in mineral and bone metabolism, which are seen as serum parathyroid hormone, calcium, and phosphorus concentration changes. Secondary hyperparathyroidism contributes to soft tissue and vascular calcification, cardiovascular morbidity, and the risk of death [2–4].

Drugs, including active vitamin D, are the main form of therapy for mild-to-moderate secondary hyperparathyroidism. Parathyroidectomy (PTX) is an effective therapy for severe secondary hyperparathyroidism [5–7]. However, some patients, especially those with cardiopulmonary insufficiency, cannot tolerate this surgery. Thus, microwave ablation (MWA), a minimally invasive procedure, has been used to treat severe secondary hyperparathyroidism [8,9], especially in patients who cannot tolerate parathyroidectomy. MWA has advantages over PTX [10], namely minimal invasiveness, ease of administration, and rapid recovery, and MWA has achieved good results in patients with severe secondary hyperparathyroidism [11–13]. However, some studies have shown that MWA is less effective than PTX for severe secondary hyperparathyroidism [14,15]. Additionally, most
studies have reported only the short-term results of MWA, generally those within 29 months [11,16,17]. Thus, the long-term results of MWA for severe secondary hyperparathyroidism have not yet been conclusively established.

In the present multicenter retrospective cohort study, we compared the clinical outcomes of MWA and PTX for severe secondary hyperparathyroidism undergoing hemodialysis.

Materials and methods

Study design

This multicenter retrospective cohort study involved four hospitals. The study cohort comprised all patients with secondary hyperparathyroidism and end-stage renal disease who underwent MWA or PTX between 1 January 2010 and 31 March 2019. The participants were divided into two groups according to the initial therapy as MWA and PTX groups.

This study was approved by the Bioethics Committee of our institution, Beijing Friendship Hospital, Capital Medical University (Code: 2020-P2-023-01). Ethical approval exempts informed consent.

Patient cohort

The inclusion and exclusion criteria were as follows. Inclusion criteria were (a) age: 18–80 years, (b) hemodialysis thrice weekly for ≥6 months, (c) hyperparathyroidism secondary to end-stage renal disease, (d) intact parathyroid hormone (iPTH) concentration >800 pg/mL before initial MWA or PTX, and (e) follow-up duration of >12 months. In accordance with the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [18], severe hyperparathyroidism was defined as persistent serum iPTH concentrations of >800 pg/mL. Exclusion criteria were (a) history of MWA or PTX before January 2010, (b) history of thyroidectomy before or during the study period, and (c) lost iPTH data for more than 20% of the follow-up time points.

Intervention

Participants were treated initially with MWA or PTX and then with the treatment specified by the clinical practice guidelines. Participants could be retreated with MWA or PTX if necessary.

MWA, a form of thermal ablation, can generate very high temperatures very quickly, and the high temperatures can destroy targeted cells. The MWA procedure has been reported previously [9]. Briefly, the microwave therapy apparatus was a KY2000 ablation system (Nanjing Kangyou Applied Research Institute, Nanjing, China) operating at a frequency of 2450 MHz and equipped with a 2-mm outside diameter antenna with a 5-mm tip. The patient’s neck was sterilized and local anesthesia using 2% lidocaine hydrochloride was applied. Next, 5 ml of 2% lidocaine hydrochloride was diluted in 15 ml of normal saline and injected into the area around the parathyroid nodule to develop a heat insulation layer. Thereafter, an ablation needle was inserted into the parathyroid tissue for ablation under ultrasound guidance (Figure 1). Ablation was then performed with MWA power set between 25 and 35 Watts according to the target nodule size.

PTX was performed under general anesthesia in operating rooms and comprised one of the following three surgical procedures: total PTX, total PTX with auto-transplantation, and subtotal PTX [19].

Clinical data collection and follow-up

Baseline data for patients’ age, sex, dialysis vintage, iPTH concentrations, and treatment procedure were collected. Serum iPTH, calcium, and phosphorus concentrations were collected at the following time points: baseline, Month 1 (±2 weeks), Month 3 (±2 weeks), Month 6 (±1 month), and then at 6-month intervals (±1 month) until Month 60 or death, kidney transplantation, or transfer to another facility.

Figure 1. Parathyroid nodule presenting as a hypoechoic signal before MWA (a); the ablation needle was inserted into the parathyroid nodule under ultrasound guidance (b). MWA: microwave ablation.
Endpoints
The primary endpoint was the proportion of patients with iPTH concentrations of 100–600 pg/mL during the efficacy assessment phase (Month 6 to Month 60 or death, kidney transplantation, or transfer to another facility). The target range of iPTH concentration was in accordance with the Kidney Disease Improving Global Outcomes Guideline [20], which specify maintaining iPTH concentrations within a range of approximately two to nine times the upper limit of normal for the assay. The upper limits of normal for iPTH differed between the four participating hospitals, with two to nine times the upper limit ranging from approximately 100–600 pg/mL. The secondary endpoints were (a) differences in iPTH concentrations over time between the two groups and (b) decreases in iPTH concentrations over time in the two groups.

Other study variables
Changes in serum calcium and phosphorus concentrations over time were also analyzed in this study.

Adverse events
(i) Low serum iPTH concentration and hypocalcemia were assessed in this study. Low serum iPTH was defined as mean iPTH concentration <100 pg/mL during the efficacy assessment phase. Hypocalcemia was defined as serum calcium >2.1 mmol/L at baseline and decreasing to <2.1 mmol/L at any time point within the first 6 months after the initial MWA or PTX.

(ii) All-cause death during the study period.

Statistical analysis
All data were analyzed according to the intention-to-treat principle. All continuous variables with a normal distribution are reported as the means and standard deviations. Variables with a non-normal distribution are reported as medians and interquartile ranges. Categorical variables are reported as frequencies.

Independent t-tests were used to compare variables with a normal distribution between the two groups, namely age, dialysis vintage, and baseline iPTH concentrations. The Mann–Whitney U test was used when the distribution was skewed, which was the case for the number of parathyroid nodules, diameter of parathyroid nodules, and follow-up time. The proportion of iPTH concentrations within the 100–600 pg/mL range was compared between the two groups using Fisher’s exact test. Because there were repeated measurement data during the efficacy assessment phase, a mixed linear model was used to compare serum iPTH, calcium, and phosphorus concentrations between the groups during the efficacy assessment phase.

Cumulative incidence curves for all-cause death were plotted using Kaplan–Meier survival curves and were compared using log-rank tests. Cox regression models with the time (in months) after initial MWA or PTX as the time scale were used to calculate hazard ratios with 95% confidence intervals for all-cause death. Multivariable Cox models were adjusted for age, dialysis vintage, diabetes, and serum calcium, phosphorus, and iPTH concentrations.

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS version 26.0; IBM Corp., Armonk, NY).

Results
Enrollment
A total of 92 patients treated from January 2010 to March 2019 and followed-up until Month 60 were enrolled in this study; 47 in the MWA group and 45 in the PTX group. A flow chart of the study is shown in Figure 2.

Baseline characteristics
Patients’ baseline characteristics and clinical data are summarized in Table 1. Most studied variables were well balanced between the two groups. However, the dialysis vintage was shorter in the MWA group than in the PTX group, and the baseline iPTH concentration was slightly lower in the MWA group than in the PTX group.

Fewer parathyroid nodules were detected in the MWA group than in the PTX group; however, the sizes of the parathyroid nodules were comparable between the two groups. Regarding the surgical procedures, 53.3% of the patients in the PTX group underwent total PTX, while the remaining underwent subtotal PTX with auto-transplantation, or subtotal PTX (Table 2).

Endpoints
Primary endpoints: iPTH concentrations were within the target range (100–600 pg/mL) during the efficacy assessment phase in 26/47 (55.3%) patients in the MWA group and in 14/45 (31.1%) patients in the PTX group ($p = .02$). Most patients in the MWA group who did not achieve the target iPTH range had high iPTH concentrations ($\geq$ 600 pg/mL), whereas most patients in the PTX group whose values were not in the target range had low iPTH concentrations (< 100 pg/mL, Table 3).

Secondary endpoints: (1) Mean iPTH concentrations during the efficacy assessment phase were significantly higher in the MWA group than in the PTX group ($649 \pm 519$ pg/mL versus $136 \pm 228$ pg/mL, respectively; $p < .01$; Figure 3(a)). (2) The decreases from baseline over time in mean iPTH concentration during the efficacy assessment phase were significantly smaller in the MWA group than in the PTX group, with mean decreases in iPTH concentration from baseline of $725 \pm 605$ and $1369 \pm 478$ pg/mL in the MWA and PTX groups, respectively ($p < .01$; Figure 3(b)).
Baseline serum calcium and phosphorus concentrations were both comparable between the two groups. Serum concentrations of both calcium and phosphorus decreased after the initial MWA or PTX; however, the concentrations of both

### Table 1. Patients’ baseline characteristics.

| Parameter                                      | Microwave Ablation n = 47 | Parathyroidectomy n = 45 | p Value |
|------------------------------------------------|---------------------------|--------------------------|---------|
| Age, mean (SD), year                          | 53.3 ± 10.8               | 51.6 ± 11.0              | .45     |
| Women, No. (%)                                | 24 (51.1)                 | 22 (48.9)                | .84     |
| Dialysis vintage, mean (SD), year             | 8.2 ± 3.4                 | 10.1 ± 5.1               | .048    |
| Diabetic, No. (%)                             | 6 (12.8)                  | 6 (13.3)                 | .94     |
| Baseline iPTH, pg/mL                          | Median (IQR)              |                          |         |
|                                                | 1287 (965–1717)           | 1446 (1103–1900)         |         |
|                                                | Mean (SD)                 |                          |         |
|                                                | 1374 ± 429                | 1505 ± 450               |         |
| Calcium, mean (SD), mmol/L                    | 2.38 ± 0.28               | 2.48 ± 0.26              | .09     |
| Phosphate, mean (SD), mmol/L                  | 2.09 ± 0.51               | 2.1 ± 0.62               | .92     |
| Follow-up time, mean (SD), month              | 46 ± 17                   | 39 ± 18                  | .03     |
| IQR: interquartile range; No.: number; iPTH: intact parathyroid hormone; SD: standard deviation.

### Table 2. Characteristics of the parathyroid nodules and treatment received.

| Parameter                                      | Microwave Ablation n = 47 | Parathyroidectomy n = 45 | p Value |
|------------------------------------------------|---------------------------|--------------------------|---------|
| No. of nodules*, per patient                   | 2 (2–3)                   | 3 (2–4)                  | .14     |
| No. of nodules ablated*, per patient           | 2 (1–2)                   | NA                       | NA      |
| Size of nodules*, cm                           |                           |                          |         |
| Maximum diameter                               | 1.2 (0.8–1.6)             | 1.2 (0.9–1.6)            | .48     |
| Minimum diameter                               | 0.7 (0.6–0.9)             | 0.6 (0.5–1.0)            | .16     |
| Type of parathyroidectomy                      | NA                        | NA                       |         |
| Total PTX, No. (%)                             | 24 (53.3)                 | 24 (53.3)                | .16     |
| Total PTX with AT, No. (%)                     | 14 (31.1)                 | 14 (31.1)                |         |
| Subtotal PTX, No. (%)                          | 7 (15.6)                  | 7 (15.6)                 |         |

*Median (IQR).
No.: number; PTX: parathyroidectomy; Total PTX with AT: total parathyroidectomy with auto-transplantation.

### Table 3. Proportion of patients achieving and not achieving the target range iPTH concentration by treatment group.

| iPTH level (pg/mL) | Microwave Ablation n = 47 | Parathyroidectomy n = 45 |
|--------------------|---------------------------|--------------------------|
| 100–600, No. (%)   | 26 (55.3)                 | 14 (31.1)                |
| <100, No. (%)      | 1 (2.1)                   | 30 (66.7)                |
| ≥600, No. (%)      | 20 (42.6)                 | 1 (2.2)                  |

iPTH: intact parathyroid hormone; No.: number.

### Other studied variables

Baseline serum calcium and phosphorus concentrations were both comparable between the two groups. Serum concentrations of both calcium and phosphorus decreased after the initial MWA or PTX; however, the concentrations of both
parameters increased within 6 months and fluctuated during follow-up in both groups (Figure 3(c,d)).

Adverse events

(1) The proportions of patients with low serum iPTH concentrations and hypocalcemia were much higher in the PTX group than in the MWA group (Table 4). Of the 30 patients with low serum iPTH concentrations in the PTX group, 60% (18/30) underwent total PTX, 30% underwent (9/30) total PTX with auto-transplantation, and 10% (3/30) underwent subtotal PTX.

(2) All-cause death: Fifteen patients died during the study. The cumulative incidence of all-cause death was comparable between the two groups ($p = .61$ by the log-rank test; Figure 4). The multivariable-adjusted hazard ratio for all-cause death was also comparable between the MWA and PTX groups ($p = .37$; hazard ratio: 1.72, 95% confidence interval [CI]: 0.53–5.62).

Discussion

In this study, in our cohort of patients with severe secondary hyperparathyroidism undergoing hemodialysis, MWA more frequently achieved iPTH concentrations within the target range compared with PTX (57.4% versus 31.1%, respectively), and MWA rarely resulted in low serum parathyroid hormone concentrations. This finding is consistent with those of a
In the present study, we found a comparable cumulative incidence of all-cause death in the MWA and PTX groups; however, iPTH concentrations were significantly lower after MWA than after PTX. We consider the major reasons for this are as follows: First, in the present study, MWA more frequently achieved iPTH concentrations within the target range compared with PTX. The target ranges for iPTH differ between published guidelines [20,27], with the maximums ranging between 60 pg/mL and 600 pg/mL. iPTH concentrations less than 600 pg/mL may not be associated with increased mortality; only very high iPTH concentrations are reportedly associated with an increase in mortality [28,29]. In this study, although mean iPTH concentrations were significantly higher after MWA than after PTX (649 ± 519 pg/mL versus 136 ± 228 pg/mL, respectively; \( p < .01 \)), few patients still had very high iPTH concentrations after MWA. Second, MWA rarely resulted in low serum iPTH concentrations, whereas PTX was more likely to result in low serum iPTH concentrations. Some researchers have suggested that very low iPTH (<50 pg/mL to 65 pg/mL) can be associated with increased mortality [30,31].

This study has several limitations. First, information for some adverse events, such as hoarseness, and muscle spasms, was not available in this retrospective study. The only adverse events we assessed were low serum iPTH concentrations and hypocalcemia, which were data available from the hospital records. Second, the small size of the study sample may have skewed the results; larger studies are needed to assess efficacy and safety. Third, this was a retrospective study; thus, treatment was not randomly allocated. Some patients with higher numbers of parathyroid nodules may have been inclined to undergo treatment by PTX. This may have caused selection bias, which may have affected our findings.

In conclusion, MWA more frequently achieves sustained serum iPTH concentrations within the range of 100-600 pg/mL compared with PTX in patients with severe secondary hyperparathyroidism undergoing hemodialysis, and rarely results in low serum parathyroid hormone concentrations. Ultrasound-guided percutaneous microwave ablation is a promising and minimally invasive means of treating severe secondary hyperparathyroidism.

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Figure 4. Kaplan–Meier survival curves for patients with severe hyperparathyroidism who underwent microwave ablation or parathyroidectomy. There was no significant difference in the cumulative incidence of all-cause death between the microwave ablation and parathyroidectomy groups (\( p = .61 \), log-rank test).

This previous single-center retrospective cohort study [16] of 33 patients who underwent MWA and 48 who underwent parathyroidectomy. In the study, the recommended goal for iPTH concentration was achieved significantly more often in the MWA group than in the PTX group at 24 months (81.82% versus 52.63%, respectively), and persistently low iPTH concentrations were found more often in the PTX group (64.6%) than in the MWA group (0%) [16]. Our study confirmed these results. However, our efficacy outcome was the average of multiple iPTH measurements during the efficacy assessment phase, whereas in the above-cited study, the efficacy outcome was the iPTH concentration at a single timepoint. We consider an average of iPTH concentrations over time preferable because the effect of iPTH on prognosis is long-term, not short-term. In another retrospective study [14], 18/30 patients underwent MWA, and 12/30 underwent PTX. The authors reported that the recommended goal for iPTH concentration was achieved less frequently in the MWA group than in the PTX group at Month 29 (22.2% versus 50.0%, respectively). This result is inconsistent with ours; the following are possible explanations for this discrepancy. First, our efficacy outcome was the average of multiple iPTH measurements, whereas in the above-cited study, the efficacy outcome was the iPTH concentration at a single timepoint. Second, the sample size in the previous study was small (30 patients) and the longest follow-up time was 29 months. In the present study, the sample size was larger (92 patients), and the follow-up time was longer. These differences in sample size and follow-up time may have led to bias. Third, in the present study, eight non-responsive patients in the MWA group underwent PTX during the efficacy evaluation period, which may have affected the response rate.

Both MWA and PTX have been used to treat patients with severe secondary hyperparathyroidism [15,21]. PTX is commonly considered to reduce mortality in patients with secondary hyperparathyroidism undergoing hemodialysis [21–26]. However, whether MWA is associated with long-term survival benefit in such patients has rarely been investigated.
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