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Achievement of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative: recommended serum calcium, phosphate and parathyroid hormone values with parathyroidectomy in patients with secondary hyperparathyroidism

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Purpose: The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) 2003 has established guidelines for the treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease – minerals and bone disorder (CKD-MBD). This study evaluated parathyroidectomy in SHPT patients for the achievement of the NKF-K/DOQI-recommended values of serum calcium, phosphate, and parathyroid hormone (PTH).

Methods: Between January 2005 and December 2010, parathyroidectomy was performed as recommended by the NKF-K/DOQI guidelines in 81 patients with SHPT and CKD-MBD. Serum PTH, calcium, and phosphate levels were measured prior to and 6, 12, 36, and 60 months after parathyroidectomy.

Results: Calcium, phosphate, and PTH levels dropped shortly after parathyroidectomy; however, a slight increase showed in the long term. Calcium levels increased for up to 60 months. Phosphate and PTH levels increased for up to 36 months but tended to decrease slightly at 60 months. The mean values were within the target ranges, except for PTH at 36 months. The target parameters of serum phosphate (42.9–61.1% of patients) and serum calcium (a peak of 61.1% of patients at 36 months, but only 28.6% at 60 months) were achieved the most. Less than 34% of patients achieved the recommended range for PTH.

Conclusion: Parathyroidectomy was not an optimal procedure for achieving all the biochemical parameters recommended by the NKF-K/DOQI. Although it was helpful in attaining the recommended values for serum calcium and phosphate in SHPT patients resistant to medical therapy, the PTH levels did not fall within the recommended range.

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INTRODUCTION

It has been established that interrupted mineral metabolism in patients with chronic kidney disease – minerals and bone disorder (CKD-MBD) and secondary hyperparathyroidism (SHPT) plays an important role in cardiovascular disease [1,2]. To prevent or alleviate metabolic bone disease in dialysis patients with CKD-MBD thereby reducing their risk of cardiovascular disease and improving their prognosis,

the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) published the Clinical Practice Guidelines for CKD-MBD and recommended target ranges for serum calcium (8.4–9.5 mg/dL), phosphate (3.5–5.5 mg/dL), and parathyroid hormone (PTH, 150–300 pg/mL) [3]. Despite traditional SHPT treatments using dietary phosphate restriction, phosphate binders, calcium supplementation, and vitamin D sterols and the introduction of cinacalcet during the last decade, numerous observational studies have emphasized the high prevalence of cases not reaching the biochemical ranges recommended by the NKF-K/DOQI [4-7]. Despite the higher cost of cinacalcet compared to parathyroidectomy, evidence regarding long-term superiority of cinacalcet therapy is lacking [8-10]. The aim of this study was to evaluate the short-term and long-term effectiveness of parathyroidectomy in order to attain the NKF-K/DOQI-recommended values for serum PTH, calcium, and phosphate in Korean dialysis patients with CKD-MBD and uncontrolled SHPT.

METHODS

Between January 2005 and December 2010, parathyroidectomy was performed as recommended in the NKF-K/DOQI guidelines in 81 patients with SHPT and CKD-MBD most of whom were referred to our hospital from several dialysis units. Clinical, biochemical, and radiological signs of SHPT were evident in each patient. All had extremely elevated PTH levels (>800 pg/mL) and had undergone unsuccessful treatment attempts with calcimimetics, dietary phosphate restriction, phosphate binders, calcium supplementation, or vitamin D sterols. Sixty-five patients had severe persistent hypercalcemia or hyperphosphatemia and 19, 25, and 13 also suffered from intractable pruritus, bone pain, and pathologic bone fracture, respectively. Parathyroidectomy (total, 57; subtotal, 24) was performed, with exploration of the neck initially focusing on the usual anatomic sites that harbor the upper and lower parathyroid glands bilaterally. If supernumerary glands were discovered during this dissection, these were also excised. All excised specimens from suspected supernumerary glands were identified as parathyroid glands by frozen section biopsy. However, if fewer than 4 parathyroid glands were located during this process, the search for the remaining parathyroid glands proceeded by systematic sequential ipsilateral dissection of the thymus; level VI clearance; and sequential opening of the retropharyngeal space, retroesophageal space, and carotid sheath. All procedures were performed by the same surgeon. In cases where enlargement of 3 or 4 glands was noted, a subtotal or total parathyroidectomy with autotransplantation was carried out. For subtotal parathyroidectomy, 3 glands were completely removed, and approximately 50% of the smallest and most normal-appearing gland (fourth gland) was left in the neck. For total parathyroidectomy, all glands were removed during the autotransplantation, and 10–15 1-mm pieces of the smallest gland were simultaneously autotransplanted in the forearm. Postoperative follow-ups were scheduled on a regular basis to check biochemical and clinical outcomes. Postoperative complications were one bleeding and the other wound infection in all two patients. Serum PTH, calcium, and phosphate levels were measured prior to and 6, 12, 36, and 60 months after the operation. The NKF-K/DOQI-recommended values for the measured parameters were achieved and sustained. PTH analyses were carried out with the Roche Elecsys System 2010 electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Data analysis was performed using R ver. 2.5.1 (http://www.r-project.org). In addition to standard descriptive statistics and graphs for longitudinal data, for each of the 3 outcome measures (calcium, phosphate, and PTH) we fit a generalized linear mixed model that included parameters for the covariates to take into account the dependence over time of the observations from the same subject. The covariates were time of observation, dialysis duration, age, sex, and baseline serum levels. Preoperative and postoperative values were compared using the McNemar test. P-values less than 0.05 were considered significant.

RESULTS

The male-to-female ratio was 1.1:1. The average age at the time of surgery was 45.9 years for men and 51.3 years for women. The average length of follow-up was 40.0 (± 25.1) months (median, 54 months; range, 12 to 95 months). Table 1 summarizes clinical and biochemical data at the time of surgery. High PTH values (1,605.6 ± 75.8 pg/mL) were evident, together with similarly increased mean values of calcium (10.5 ± 0.1 mg/dL) and phosphate (6.1 ± 0.2 mg/dL).

We currently have 6-month and 12-month follow-up data for all patients; 36-month and 60-month follow-ups have

Table 1. Clinical and biochemical characteristics of patients (n = 81)

Characteristic	Value
Sex (male/female)	43/38
Age (yr)	48.5
Dialysis duration (yr)	12.6 ± 0.6
Parathyroid hormone (pg/mL)	1,605.6 ± 75.8
Calcium (mg/dL)	10.5 ± 0.1
Phosphate (mg/dL)	6.1 ± 0.2

Values are presented as mean ± standard deviation.

been completed for 18 and 7 patients, respectively. In fact, 65 cases are considered lost to follow-up, due to patient transfer to local clinics, and others have been censored because of renal transplantation (n = 5) or death (n = 4).

Preoperative PTH level was higher than recommended in all patients, which is in accordance with indications for surgical treatment. At 6-month and 12-month follow-up, PTH levels at or below the recommended ranges were achieved for 75.3% (n = 61) and 69.1% (n = 56) of patients, respectively. At the last follow-up, the serum PTH concentration was equal to or below the lower limit of the recommended ranges in 5 patients (71.4%, 5 out of 7) (Fig. 1). The box-plot graph (Fig. 2) illustrates substantial stability within 12 months, followed by mild increment. In fact, the generalized linear mixed model estimated a positive role for time ($P < 0.001$). In contrast, we found no significant association for covariates like sex, age, and dialysis duration.

Preoperative serum calcium was within the recommended range in 11 patients (13.6%) (Fig. 1). The percentage of patients with values within the recommended range was significantly lower before the operation compared to 6 (38.3%, n = 31) and 12 (39.5%, n = 32) months after the operation ($P = 0.0008$ and $P = 0.0002$, respectively). At 36 months after parathyroidectomy, 11 patients (61.1%) had achieved calcium levels within the recommended range; this was not significantly greater than the percentage of patients in the target range at preoperative assessment ($P > 0.05$), probably because a large number of patients were lost to follow-up. The box-plot graph (Fig. 3) suggests that the proportion increased mainly from postoperative month 36 to postoperative month 60. The generalized linear mixed model estimated positive roles for time and dialysis duration ($P < 0.001$ and $P = 0.003$, respectively) and no role for covariates like sex and age.

At 6 months after parathyroidectomy, 40 patients (49.3%)

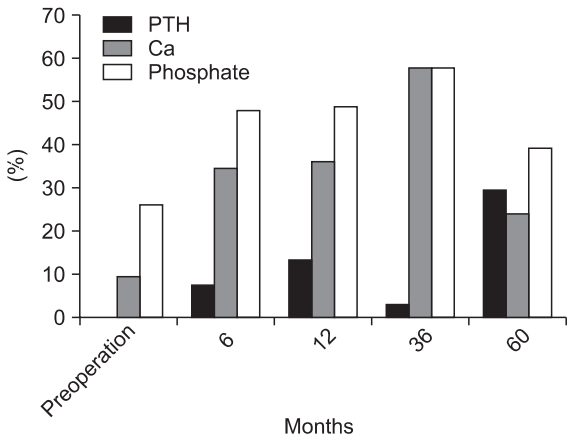

Fig. 1. Percentage of patients with persistent postoperative parathyroid hormone (PTH), calcium (Ca), and phosphate levels within the recommended ranges.

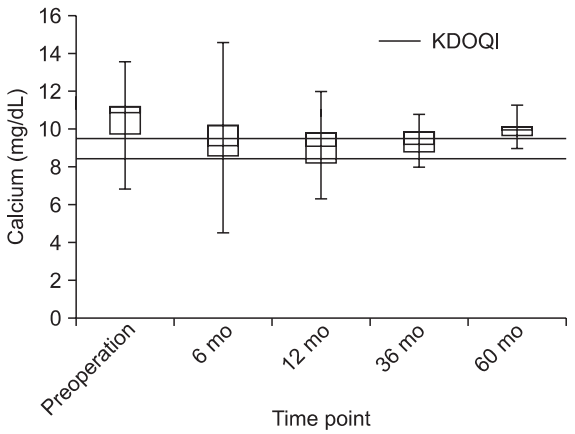

Fig. 3. Box-plot graph of serum calcium levels after parathyroidectomy. KDOQI, Kidney Disease Outcomes Quality Initiative.

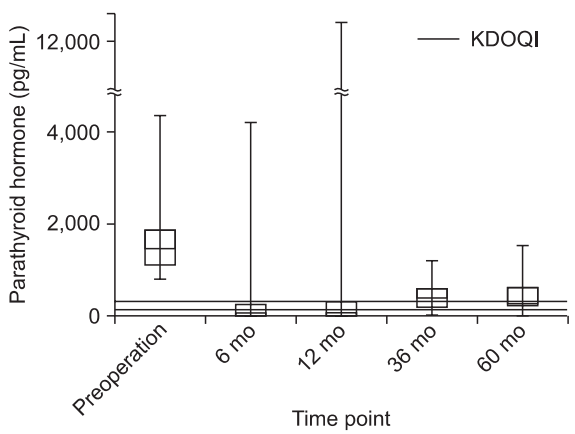

Fig. 2. Box-plot graph of parathyroid hormone levels after parathyroidectomy. KDOQI, Kidney Disease Outcomes Quality Initiative.

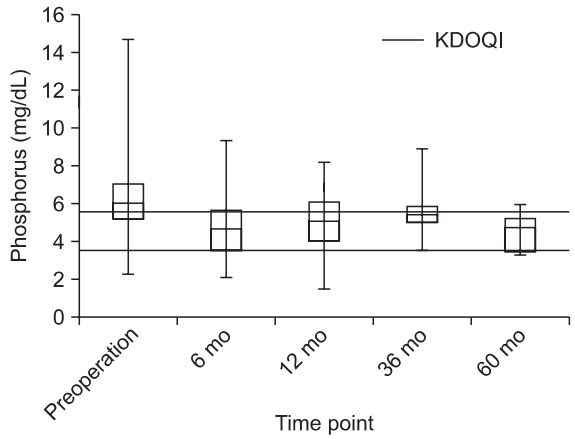

Fig. 4. Box-plot graph of serum phosphate levels after parathyroidectomy. KDOQI, Kidney Disease Outcomes Quality Initiative.

had achieved recommended values for phosphate (P = 0.0195), and at 12 months, 42 patients (51.8%) had reached the target range for phosphate concentration (P = 0.0115) (Fig. 1). The box-plot graph (Fig. 4) illustrates a mild increment of PTH and phosphate values during the first 36 months and a decrement by 60 months after parathyroidectomy. The generalized linear model estimated positive roles for time and dialysis duration (P = 0.0005 and P = 0.0059, respectively), similar to calcium. Covariates like sex and age were not statistically significant.

DISCUSSION

The most difficult NKF-K/DOQI parameter to achieve was serum PTH level; only 1 patient had a PTH level within the target range at 36 months after parathyroidectomy. Mazzaferro et al. [11] reported that only 9.1% of patients attained PTH values within the NKF-K/DOQI range at 12-month follow-up. More than one half of our patients had PTH values below 150 pg/mL at 12 months after surgery; such levels might suggest low-turnover bone disease, although several studies have underlined a lack of correlation between PTH levels and low-turnover bone disease [12,13].

The morbidity associated with severe hypoparathyroidism remains debatable. Several studies explain that these patients continue cholecalciferol and calcium replacement therapy; severe hypoparathyroidism is not likely to cause significant changes in bone mineral density, symptomatic hypocalcemia, or increased morbidity and mortality [14-17]. For this reason, it was not permitted to decide the parathyroidectomy in SHPT as successful, and it is considered to select different thresholds for classifying persistence, recurrence or even hypoparathyroidism following individual standards empirically. Gagne et al. [18], Tominaga et al. [19], and Coen et al. [20] suggested that the same PTH range generally recommended for CKD-MBD patients should also be recommended after parathyroidectomy.

Our data indicate that after parathyroidectomy, PTH levels usually lie outside of the recommended range, while better results occur for serum calcium and phosphate. Postoperative values of all 3 variables were significantly lower than preoperative values. Serum calcium and phosphate levels were inversely associated with dialysis duration (P = 0.003 and P = 0.0059, respectively). There is a greater decrease in serum calcium and phosphate levels with a shorter period of dialysis. To our knowledge, patients with lower PTH at baseline and shorter dialysis duration were more likely to achieve NKF-K/DOQI PTH targets than those with more severe disease undergoing cinacalcet-based medical treatment, although the literature contains no study about the relationship of parathyroidectomy and dialysis duration [21]. The severity of SHPT seems to have an effect on the achievement of NKF-K/DOQI ranges after parathyroidectomy, however, further investigations are needed.

According to the NKF-K/DOQI recommendation for PTH levels, cinacalcet-based medical treatment had better outcomes than parathyroidectomy, achieving the target range in one-third of patients during 6 months of treatment [22]. Additionally, recommended values were reached in 21% of patients with severe SHPT (PTH > 800 pg/mL) after 1 year [21]. Despite its suboptimal PTH outcomes, parathyroidectomy had a significant and favorable effect on calcium and phosphate levels, which reached the NKF-K/DOQI target ranges in 55.8% and 60.5% of patients, respectively. These results are comparable to if not better than those of cinacalcet-based medical treatment, which achieved target levels of calcium and phosphate in 49–51% and 33–48%, respectively [21,22]. However, a study has shown that parathyroidectomy was extremely effective in producing significant reduction in PTH: 96% of patients treated surgically achieved PTH ≤ 300 ng/dL after 18 months, compared to 21% of patients who received cinacalcet prescriptions. Neither intervention significantly altered the mean serum calcium or phosphate levels [23]. Further multicenter studies are needed to assign more definitive roles to parathyroidectomy and cinacalcet.

A limitation of our study was that many patients were lost to follow-up. As the services related to dialysis are better at local clinics than at tertiary hospitals, CKD patients prefer the former. Consequently, we only have long-term follow-up data for a few patients, and our long-term results are not representative of the entire cohort.

In conclusion, parathyroidectomy is not an optimal procedure for achieving all the NKF-K/DOQI biochemical parameters. It is helpful in attaining NKF-K/DOQI-recommended values for serum calcium and phosphate, but not serum PTH. Further investigation is required to elucidate the clinical consequences of our findings.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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