

# Parathyroidectomy: Complex Decisions about a Complex Procedure

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Patients on maintenance dialysis with severe secondary hyperparathyroidism (SHPT) present a complex clinical challenge. Despite decades of study, the role of parathyroidectomy (PTX) in the management of SHPT remains uncertain. In theory, PTX occupies a well defined space: to paraphrase Kidney Disease Improving Global Outcomes (KDIGO) guideline 4.2.5, individuals with high levels of parathyroid hormone (PTH) refractory to medical treatment should be referred for consideration of surgery (1,2). In reality, the nephrology community continues to grapple with how to best use PTX to treat severe PTH elevations.

The intriguing origins of PTX are recounted in several accounts that are well worth reading (3,4). There is some controversy about when the procedure was first performed, but PTX for the indication of osteitis fibrosa cystica seems to have first been undertaken in Vienna in 1925 by Felix Mandl (5). PTX for SHPT may have been first reported in 1960, when two patients with “renal failure” underwent subtotal PTX (6). PTX seems to have entered the mainstream for patients on dialysis by the 1990s accompanied by the admonition that “...the most important factor in the outcome of surgery is to have a highly skilled surgeon experienced in parathyroid surgery” (7)—sound advice regarding this complex procedure.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Kim *et al.* (8) report changes in PTX rates in patients on maintenance dialysis from 2002 to 2011. Kim *et al.* (8) find that rates declined sharply in 2004 and 2005 before increasing again and stabilizing from 2006 to 2011. To fully appreciate their findings, however, we must first consider them within the broad historical trends in PTX and contextualize them within the framework of seminal events that have shaped SHPT management, such as the introduction of new medications, the formulation of new clinical practice guidelines, and the publication of key studies.

Several essential epidemiologic studies provide an important backdrop to the investigation by Kim *et al.* (8). Kestenbaum *et al.* (9), in an early study, reviewed PTX rates from 1990 to 1999. Kestenbaum *et al.* (9) found that adjusted PTX rates were relatively stable at approximately 9–10/1000 patient-years from 1990 to 1995 and then, decreased fairly sharply, reaching a nadir of about 6/1000 patient-years in 1998.

Kestenbaum *et al.* (9) speculated that this decline might have been because of widespread adoption of intravenous calcitriol and an “increased awareness of SHPT as a multi-system disease,” although they did not have access to patient-level or aggregate data on PTH levels or calcitriol prescription rates (9). Foley *et al.* (10) then extended follow-up to 2002, confirming the finding of a nadir in 1998, but also reporting a new peak of nearly 12/1000 patient-years in 2002. Foley *et al.* (10) were uncertain as to why this increase occurred, especially because new formulations of intravenous vitamin D sterols were being introduced (11). A follow-up study (12), examining trends out to 2007, showed an abrupt decrease in 2004–2006 and a nadir at <6/1000 patient-years in 2005, during which time approximately 90% of patients were receiving intravenous vitamin D sterols. Somewhat presciently, Li *et al.* (12) speculated that the decrease in 2004–2006 might have been because of the introduction of cinacalcet.

The most recent trends reported by Kim *et al.* (8) further clarify this picture. Using the National Inpatient Sample (NIS), Kim *et al.* (8) confirm that PTX rates declined sharply in 2004 and 2005, reaching a nadir of about 3.3 procedures per 1000 patients, and that the rates increased again before becoming relatively constant at approximately 5/1000 patients from 2006 to 2011. It is important to note that differences in study designs mean that the rates are not directly comparable across all published reports, although this should not affect contextualization of broad trends. A major benefit of the NIS is that the study sample is unconstrained by insurance status, allowing observation of patients without Medicare who tend to be younger and more likely to undergo PTX than older patients. A possible weakness, however, is that the indication for PTX was uncertain; about 15% of patients underwent PTX on hospital day 2 or later, suggesting that PTX may not have been an uncomplicated elective primary procedure in their study sample (8).

Kim *et al.* (8) attribute the decrease in PTX rates in 2004 and 2005, quite reasonably, to the 2004 introduction of cinacalcet (13). During those years, speculation abounded that cinacalcet might constitute what was colloquially termed a medical PTX, perhaps rendering PTX obsolete in all but the most refractory patients. Although it is true that, many years later, cinacalcet can likely be credited with decreasing PTX rates as

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shown in a randomized clinical trial (14) and a recent meta-analysis (15), its introduction has not, as Kim *et al.* (8) show, resulted in a sustained rate decrease. This may be because randomized clinical trials, conducted in idealized environments, test efficacy and therefore, likely represent an upper limit of the performance of an intervention. Appreciation of this phenomenon has prompted calls to acknowledge the important role of pragmatic clinical trials, which often generate estimates of real world effectiveness (16,17). The issue of efficacy versus effectiveness seems particularly acute in the case of cinacalcet: for reasons that remain elusive, cinacalcet has not been used as many thought it would be, with many patients experiencing only intermittent exposure and rebounding when exposure ceases (18). This practice likely reduces cinacalcet's long-term effectiveness.

One somewhat unexpected finding is that PTX rates have not decreased substantially after the publication of the 2009 KDIGO clinical practice guidelines on CKD-mineral and bone disorder, which greatly liberalized the acceptable PTH target range (1). Large dialysis providers in the United States now commonly use protocols in which the target PTH levels are between 150 and about 500–600 pg/ml. Because PTX generally seems to be reserved for patients with PTH levels >1000 pg/ml, it is likely that relatively few patients with PTH levels of 300–600 pg/ml were previously being referred for PTX; as such, the guideline change may not have had the effect of averting many PTXs.

Whether the equilibrium that has developed concerning PTX represents the optimal treatment approach is unclear. A well designed observational study could conceivably provide insights into this issue, but it would have to overcome the powerful source of confounding known as nonrandom treatment allocation. This refers to the scenario in which two patients who seem similar are actually characterized by important differences about which only the bedside physician has intimate knowledge, making comparison of like to like patients in an observational study extremely challenging. Such analyses have been attempted, sometimes from a cost-effectiveness perspective (19); future observational work should use the most advanced design and analytic approaches, such as marginal structural models, and/or techniques such as inverse probabilities of treatment and censoring weighting, to compare outcomes between patients treated with PTX and those treated medically.

Clinical practice guidelines for CKD-mineral and bone disorder are currently being revisited. In any future recommendation involving the role of PTX, several factors should be considered. First, recent work has shown that the risk-to-benefit ratio of PTX may be more unfavorable than traditionally appreciated. A nontrivial 2% mortality rate in the month after PTX was reported using data from a large national dialysis provider (20). Second, PTX, which undoubtedly reduces PTH levels enormously in most patients, seems to fail in a surprisingly large subset, and hypocalcemia remains a substantial problem in many patients even 6–12 months after surgery (21). These findings likely diminish enthusiasm for PTX. However, another finding might cast PTX in a more favorable light: a recent study examining complications of PTX for primary hyperparathyroidism ( $n > 17,000$ ) in California showed a halving of complication rates over time (22). A modest consolidation of procedures performed in high-volume centers may be partially

responsible. Although patients on dialysis were excluded from that study, experience at the level of the operative center and the individual physician would presumably have a spillover effect, conferring benefits to patients on dialysis undergoing PTX for SHPT. Third, another consideration is that patients on dialysis are living longer than ever before (23). The largest gains, as expected, are among the youngest patients, precisely those at highest risk of developing unremitting hyperparathyroidism. Fourth, the introduction of a potent calcimimetic, etacalcitide, is imminent (24,25) and will likely provide a new treatment option for patients with SHPT.

The nephrology community should engage in a robust discussion about the appropriate role of PTX in patients on maintenance dialysis with SHPT. More work is needed examining which types of patients might benefit from PTX, such as those likely to live longest, and which types might incur undue risk, such as those who are nonadherent with therapy and who may be at elevated risk of life-threatening adverse events after surgery. Tailored therapy could conceivably involve the use of noninvasive markers of bone turnover, such as alkaline phosphatase fractions, or other assessments of bone health to help determine which patients would benefit from one approach over another approach. With the substantial growth in the maintenance dialysis population in the United States and across the world, optimal treatment of severe SHPT is likely to be a major clinical issue faced by the nephrology community for the foreseeable future.

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