Surgery 169 (2021) 94–101

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Timing of parathyroidectomy for tertiary hyperparathyroidism with end-stage renal disease: A cost-effectiveness analysis

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ARTICLE INFO

Article history:
Accepted 1 June 2020
Available online 27 July 2020

ABSTRACT

Background: Tertiary hyperparathyroidism associated with end-stage renal disease is characterized by progression from secondary hyperparathyroidism to an autonomous overproduction of parathyroid hormone that leads to adverse health outcomes. Rates of parathyroidectomy (PTX) have decreased with the use of calcimimetics. Optimal timing of PTX in relation to kidney transplant remains controversial. We aimed to identify the most cost-effective strategy for patients with tertiary hyperparathyroidism undergoing kidney transplant.

Methods: We constructed a patient level state transition microsimulation to compare 3 management schemes: cinacalcet with kidney transplant, cinacalcet with PTX before kidney transplant, or cinacalcet with PTX after kidney transplant. Our base case was a 55-year-old on dialysis with tertiary hyperparathyroidism awaiting kidney transplant. Outcomes, including quality-adjusted life years, surgical complications, and mortality, were extracted from the literature, and costs were estimated using Medicare reimbursement data.

Results: Our base case analysis demonstrated that cinacalcet with PTX before kidney transplant was dominant, with a lesser cost of $399,287 and greater quality-adjusted life years of 10.3 vs $497,813 for cinacalcet with PTX after kidney transplant (quality-adjusted life years 9.4) and $643,929 for cinacalcet with kidney transplant (quality-adjusted life years 7.4).

Conclusion: Cinacalcet alone with kidney transplant is the least cost-effective strategy. Patients with end-stage renal disease-related tertiary hyperparathyroidism should be referred for PTX, and it is most cost-effective if performed prior to kidney transplant.

Introduction

Secondary hyperparathyroidism (2HPT) associated with end-stage renal disease (ESRD) is characterized by an increased production of parathyroid hormone (PTH) and subsequent parathyroid gland hyperplasia in response to a decreased excretion of phosphate and decreased absorption of calcium. In 2HPT, elevated serum PTH levels are mediated successfully by medical treatment with vitamin D analogs and calcitriol. Over time, 2HPT can progress from a physiologic hyperplasia to a pathologic, polyclonal adenomatous disease in which the parathyroid glands have decreased expression of calcium-sensing receptors and begin secreting PTH autonomously and inappropriately independent of serum calcium levels. This progression of disease to tertiary hyperparathyroidism (3HPT) is characterized by persistently and severely increased serum PTH levels (>2–9 times the upper limit of normal) that cannot be decreased with medical therapy, including vitamin D analogs and calcitriol.[1] Typically, most of these patients, but not all, will develop hypercalcemia and are at an increased risk for cardiovascular events, renal osteodystrophy, pathologic fractures, and mortality.[2] Patients with 3HPT are often identified in the setting of persistently increased levels of parathyroid hormone levels and an inability to re-establish calcium homeostasis after correction of the underlying ESRD with a successful kidney transplant (KTxp).[2-4] However, as the number of patients diagnosed with ESRD increases 5% to 7% per year, with the need for donor transplants increasing disproportionately at 8% per year, patients with ESRD are requiring dialysis for greater periods of time prior to receiving a KTxp, and the unregulated hyperparathyroidism related to 3HPT has become increasingly recognized in pretransplant renal dialysis patients as well.[1,3,4]

Presented at the 41st Annual Meeting of the American Association of Endocrine Surgeons.

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https://doi.org/10.1016/j.surg.2020.06.012
0039-6060/

Since the development of calcimimetic agents such as cinacalcet, which increases the sensitivity of the calcium receptor on parathyroid tissue, treatment of pre-KTxp patients with 3HPT has been largely medical.[2] Patients with ESRD would typically initiate treatment with cinacalcet once they progressed into 3HPT to address the hypercalcemia and/or decrease the markedly increased PTH levels. In the era of calcimimetics, parathyroidectomy (PTX) was typically avoided unless they were hypercalcemic after a successful KTxp, when patients were no longer dialysis-dependent and thought to be healthier.[3] But there are considerable data to suggest that among posttransplant 3HPT patients, this long-standing unregulated hyperparathyroidism with or without hypercalcemia can lead to delayed graft function, increased graft failure, more fractures, and greater mortality.[5] Furthermore, studies have shown that PTX before KTxp would not only be safe but could also avoid the increased risk of allograft failure.[6] Compared with medical management alone (including vitamin D analogs, calcitriol, and calcimimetic agents), PTX for patients with 3HPT pre-KTxp is associated with a greater rate of success of the KTxp, lesser all-cause mortality, and less cardiovascular mortality.[6-8]

The optimal timing for PTX among pretransplant 3HPT patients is an ongoing debate. The overall goal of our study was to compare treatment strategies for patients with pretransplant 3HPT, including cinacalcet alone with KTxp, cinacalcet with PTX before KTxp, or cinacalcet with PTX after KTxp and to determine the most cost-effective timing for PTX.

Methods

Model design

A patient-level state transition microsimulation was constructed in TreeAge Pro (TreeAge 2019, Williamstown, MA). We simulated a hypothetic cohort of 100,000 55-year-old individuals with ESRD on dialysis with 3HPT, categorized in the literature as those with a serum PTH >2 to 9 times the upper limit of normal with or without hypercalcemia, not responding to traditional medical therapy. We designated our base case as a 55-year-old, which is the average patient age from the studies we used, to control for age and allow our end points (quality-adjusted life years [QALYs] and life years) to be dependent on the various treatment strategies and associated health states. Health states in the model included 3HPT associated with ESRD on dialysis, ESRD on dialysis after correction of 3HPT with PTX, 3HPT after correction of ESRD with KTxp, chronic allograft failure, PTX failure, hypoparathyroidism, and death. The cycle duration was 1 month, and the model followed the cohort up until age 100 or death. In each cycle, the simulated patient could remain in the same health state, progress to a different health state, or die.

Management strategies

The treatment strategies in our analysis consisted of the following: cinacalcet alone with KTxp, cinacalcet with PTX before kidney transplant (P1K2), and cinacalcet with PTX after kidney transplant (K1P2). Given that our population consisted of patients with 3HPT on dialysis with markedly increased PTH levels with or without hypercalcemia, we made the assumption that these patients would be started on cinacalcet as recommended in the 2017 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines to decrease the PTH levels and treat the hypercalcemia if present.[1] Consequently, cinacalcet was included in each of the 3 strategies and patients continued on cinacalcet indefinitely or until they underwent PTX (either before or after the KTxp). If the PTX failed, the patient would re-enter the state of 3HPT and restart cinacalcet. If hypoparathyroidism occurred after PTX, patients transitioned to its corresponding health state and initiated treatment with calcitriol.

In the K1P2 strategy, 1% of patients with ESRD received a KTxp each monthly cycle. After a successful operation, the patient proceeded to PTX after a 12-month waiting period, the typical time course reported in the literature.[4] In the P1K2 strategy, all patients began with a PTX; 2 months after PTX, which we estimated to be a conservative time frame to allow for recovery, patients proceeded to a KTxp at the same 1% monthly rate.[4] If the KTxp failed, the patient transitioned to the chronic allograft failure state and had an increased risk of death due to chronic allograft failure for the first year. After the first year, their risk of death returned to the baseline risk of all-cause, age-related mortality for patients with ESRD.[9] Patients could move from any health state to death owing to all-cause, age-related, operative, or graft failure-associated mortality. Figure 1 demonstrates a simplified state transition model. To simplify the analysis, we chose to model patients who could only receive KTxp or PTX once in their lifetime.

Outcomes

The primary outcome of this analysis was the incremental cost-effectiveness ratio per quality- QALY between competing strategies. A willingness to pay (WTP) threshold of $100,000/QALY was used to determine cost-effectiveness. Secondary outcomes assessed included total lifetime cost, QALYs, unadjusted life-years (life expectancy), and allograft failure rates.

Parameter estimates and model transition probabilities

Model parameters were based on estimates from the literature. Base-case values and ranges used in sensitivity analyses are summarized in Table I.[8-23] All-cause, age-related mortality rates were calculated from the 2018 Annual Data Report of the United States Renal Data System.[4] For the P1K2 strategy, we calculated the odds of graft failure for the P1K2 strategy compared with the K1P2 strategy (0.583) by taking the inverse of the odds ratio of graft failure for the K1P2 strategy compared with the P1K2 strategy (1.715) from the analysis by Littbarski et al[5]; this odds ratio (0.583) is similar to the odds ratio calculated by Callender et al (0.547) that also compared the P1K2 strategy with the K1P2 strategy.[6] We then multiplied this odds ratio to the rate of graft failure among patients undergoing PTX posttransplant (0.0025) to obtain the estimated graft failure rate among patients undergoing PTX pretransplant of 0.0015.

Costs and utilities

Published estimates of costs from prior years were converted to 2019-year dollars using the Consumer Price Index (US Bureau of Labor Statistics). A third-party payer perspective was used for all costs. All operative procedures were treated as one-time costs, whereas cinacalcet and dialysis were considered recurring, monthly costs. Measures of QALYs were adjusted to utility scores for specific health states. For patients who had 3HPT, hypoparathyroidism, or permanent recurrent laryngeal nerve injury, utility decrements were applied as multiplicative factors to their current health state.[5] For the base-case analysis, all cost and expected life years were discounted at an annual rate of 3%.

Sensitivity analyses

We performed one-way, deterministic, sensitivity analyses on all health state transition probabilities to determine the effects of changes in individual model parameters on estimated outcomes

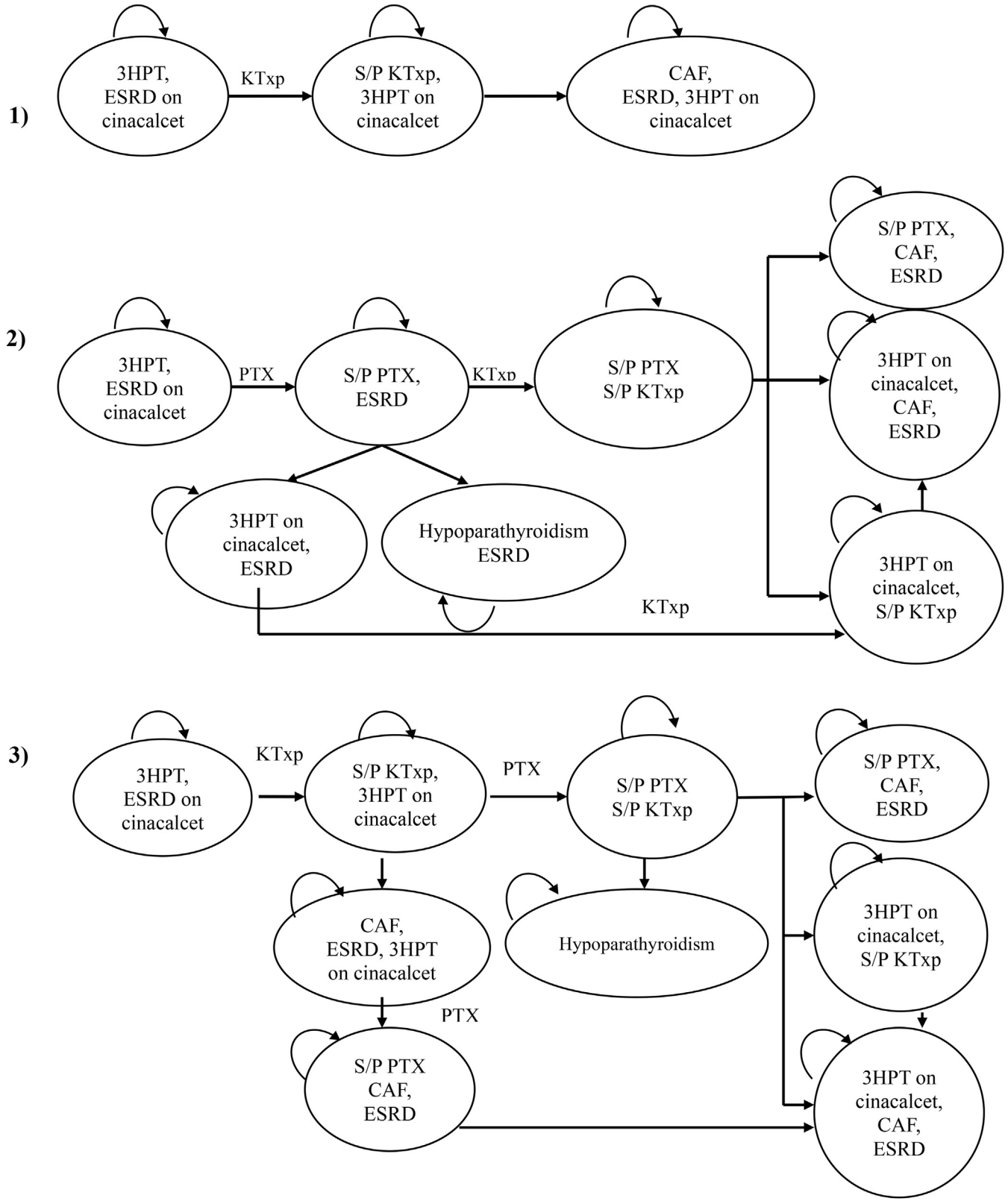

Fig 1. Simplified model of treatment strategies with health states: (1) cinacalcet + KTxp; (2) cinacalcet + PTX before KTxp (P1K2); (3) cinacalcet + PTX after KTxp (K1P2). End-stage renal disease (ESRD), tertiary hyperparathyroidism (3HPT), chronic allograft failure (CAF).

Table I
Base case values and ranges used in the sensitivity analysis

Parameter	Base-case estimate	Range used in sensitivity analysis	Distribution for PSA	References
Start age	55			
Probabilities				
All-cause mortality, ESRD	Life table			8, 9
All-cause mortality, general	Life table			9
Risk of graft failure (K1P2)	0.0025	(0.0019–0.0031)	β	10
Risk of graft failure with 3HPT	0.0092	(0.0069–0.0115)	β	5
Risk of graft failure (P1K2)	0.0015	(0.0011–0.0018)	β	5, 10
Risk of death from graft failure	0.0150	(0.0113–0.0188)	β	11
KTxp surgical mortality risk	0.005	(0.0037–0.0062)	β	12
PTX surgical mortality risk (K1P2)	0.004	(0.0030–0.0050)	β	13
PTX surgical mortality risk (P1K2)	0.02	(0.015–0.025)	β	14
Monthly KTxp rate for ESRD patients	0.0101	(0.0076–0.0126)	β	4
PTX failure (K1P2)	0.013	(0.0098–0.0163)	β	15
PTX failure (P1K2)	0.045	(0.0338–0.0563)	β	16
Risk of hypoparathyroidism s/p PTX (K1P2 and P1K2)	0.005	(0.0038–0.0063)	β	17
Risk of unilateral RLN injury s/p PTX	0.0077	(0.0058–0.0096)	β	18
Risk of bilateral RLN injury s/p PTX	0.0039	(0.0029–0.0049)	β	18
Utilities				
ESRD	0.61	(0.51–0.71)	β	19
3HPT	0.85	(0.75–0.95)	β	14
Hypoparathyroidism	0.894	(0.794–0.994)	β	20
Unilateral RLN injury	0.89	(0.79–0.99)	β	21
Bilateral RLN injury	0.21	(0.11–0.31)	β	21
Post KTxp	0.82	(0.72–0.92)	β	19
Costs				
Cost of KTxp	82,283.66	(61,712.75–10,2854.58)	γ	19
Monthly costs for 1st year post KTxp	4,002.85	(3,002.14–5,003.56)	γ	19
Cost of monthly cinacalcet	978.13	(733.60–1,222.66)	γ	14
Cost of monthly calcitriol	78.74	(39.37-157.48)	γ	20
Cost of monthly dialysis	3,892.99	(2,919.74–4,866.24)	γ	22
Cost of RLN injury treatment	12,777.62	(6,388.81–25,555.24)	γ	20
Cost of PTX	6,810.85	(5,108.14–8,513.56)	γ	14, 20
Cost of outpatient PTX services (K1P2)	2,752.93	(1,376.47–5,505.86)	γ	23
Cost of inpatient PTX services (P1K2)	5,135.40	(2,567.70–10,270.80)	γ	23

s/p, status post (after); *RLN*, recurrent laryngeal nerve.

across a range of values. We also performed a two-way sensitivity analysis of the risk of graft failure for K1P2 versus the risk ratio of graft failure for P1K2 across a range of values to validate our calculation for the risk of graft failure for the P1K2 strategy. In addition, a probabilistic sensitivity analysis was performed. Distributions for specific model parameters were assigned and 1,000 iterations and recalculations of the model were run with cohorts of 1,000 patients to further elucidate the optimal treatment strategy under uncertain conditions.

Table II
Base case analysis comparing the cost and QALY of the 3 strategies

Strategy	Cost	QALY
*Cinacalcet + KTxp	643,929	7.4
†Cinacalcet + P1K2	399,287	10.3
‡Cinacalcet + K1P2	497,813	9.4

The P1K2 strategy was dominant with the lowest cost and highest QALY.
* Cinacalcet + KTxp
† Cinacalcet + PTX before KTxp (P1K2)
‡ Cinacalcet + PTX after KTxp (K1P2)

Results

Outcomes

Our base case analysis demonstrated that cinacalcet with PTX before KTxp transplant (P1K2) was the dominant strategy. This strategy had the least total cost of $399,287 and greatest QALY of 10.3, compared with $497,813 for K1P2 (QALY of 9.4) and $643,929 for KTxp with cinacalcet alone (QALY of 7.4; Table II). Given that the P1K2 strategy had both a lesser cost and greater QALY, calculation of an incremental cost-effectiveness ratio per QALY would result in negative values and was not a suitable tool to compare strategies. P1K2 resulted in the greatest life expectancy at 14.3 years compared with K1P2 at 14.0 years. The cinacalcet alone with KTxp strategy had the least life expectancy at 12.8 years.

We ran a patient level state transition analysis comparing the 3 strategies in terms of rates of chronic allograft failure over 1, 5, 10, 15, and 20 years to verify the accuracy of our model (Table III). We confirmed that the least yearly and lifetime risk of graft failure occurred in the P1K2 group.

The one-way deterministic and probabilistic sensitivity analyses demonstrated that the model was robust to uncertainty in model parameters. Within the prescribed ranges for the base case parameters, P1K2 remained the dominant strategy at a WTP of $100,000. The threshold analysis determined that for the K1P2 strategy to become cost-effective at a WTP of $100,000, the monthly rate of chronic allograft failure in the P1K2 strategy would have to increase from 0.15% to 0.37%, the monthly rate of chronic allograft failure in the K1P2 strategy would have to decrease from 0.25% to 0.045%, the operative mortality from PTX in the P1K2 strategy would have to increase from 2% to 13.2%, or the PTX failure rate in the P1K2 strategy would have to increase from 4.5% to 32.3%. The results of the probabilistic sensitivity analysis in Fig 2 illustrate the individual cost and effectiveness pairs of 1,000 iterations and

Table III
Patient level state transition microsimulation analysis comparing the rate of chronic allograft failure over time for the 3 strategies

	Graft failure rate (%)					
	Lifetime	1 y	5 y	10 y	15 y	20 y
*Cinacalcet + KTxp	63.21	7.86	31.31	47.82	56.37	60.44
†Cinacalcet + P1K2	24.48	1.57	6.94	12.55	16.89	20.17
‡Cinacalcet + K1P2	38.35	7.86	15.25	22.87	28.68	32.93
USRDS KTxp with DDRT	-	7.2%	21.7%	53.4	-	-

* Kidney transplant (KTxp) with cinacalcet alone
† Parathyroidectomy (PTX) before KTxp with cinacalcet (P1K2)
‡ PTX after KTxp with cinacalcet (K1P2). We compared our model to the available graft failure rates for a 55- to 59-year-old patient undergoing a deceased donor renal transplantation (DDRT) from the 2019 United States Renal Data System (USRDS) Report.[25]

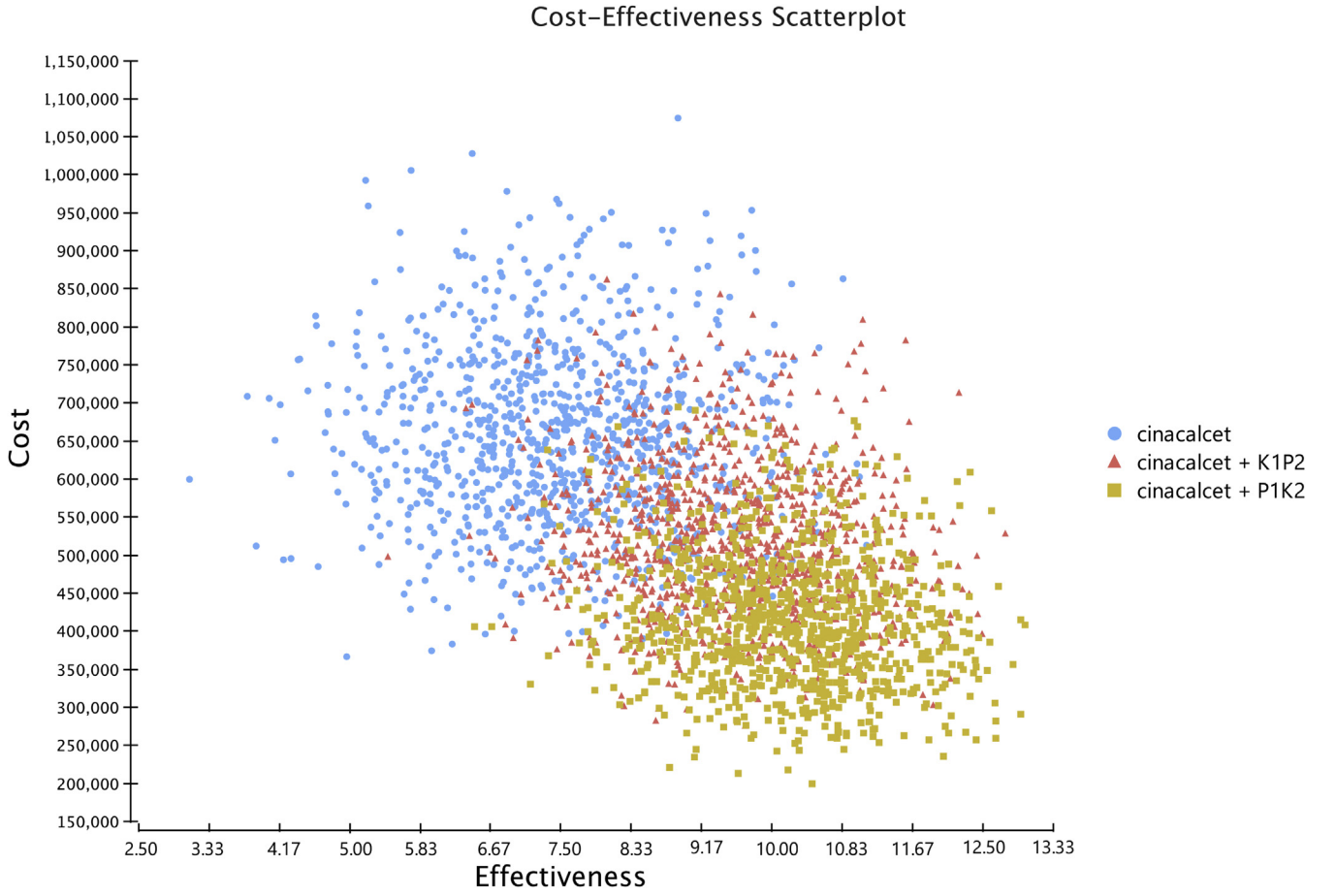

Fig 2. A probabilistic sensitivity analysis demonstrating individual cost and effectiveness pairs of 1,000 iterations and recalculations of the model with cohorts of 1,000 patients. PTX before KTxp with cinacalcet (P1K2) remained the strategy with the lowest cost and highest effectiveness.

recalculations of the model with cohorts of 1,000 patients. The cost-effectiveness acceptability curve demonstrated that the P1K2 strategy remained dominant compared with the other 2 strategies, as indicated by the plateauing of the curve as willingness to pay increases (Fig 3). At the assigned willingness to pay of 100,000, the P1K2 strategy remained cost-effective for 96.4% of iterations, whereas K1P2 was cost-effective for 3.6% of iterations. The results of the two-way sensitivity analysis of the risk of graft failure for K1P2 versus the risk ratio of graft failure for P1K2 demonstrated that the P1K2 strategy remains dominant across a range of ±25% (Fig 4, *A*); it is not until the risk ratio of graft failure for P1K2 is extended beyond 1.66 that the K1P2 strategy becomes cost-effective (Fig 4, *B*).

Discussion

To our knowledge, our study is the first to compare the cost-effectiveness of 3 different treatment strategies to manage 3HPT in ESRD patients: (1) cinacalcet alone followed by KTxp, (2) cinacalcet followed by early PTX then KTxp, and (3) cinacalcet followed by KTxp and late PTX. Our results confirm that treatment of 3HPT with cinacalcet alone is a less cost-effective strategy compared with cinacalcet with PTX. As demonstrated in Table II, the differences in cost and QALYs are greater when comparing the cinacalcet alone with KTxp strategy with either strategy that includes KTxp with PTX. This conclusion is supported by a cost-effectiveness analysis by Naryan et al[14] that demonstrated that PTX was less expensive

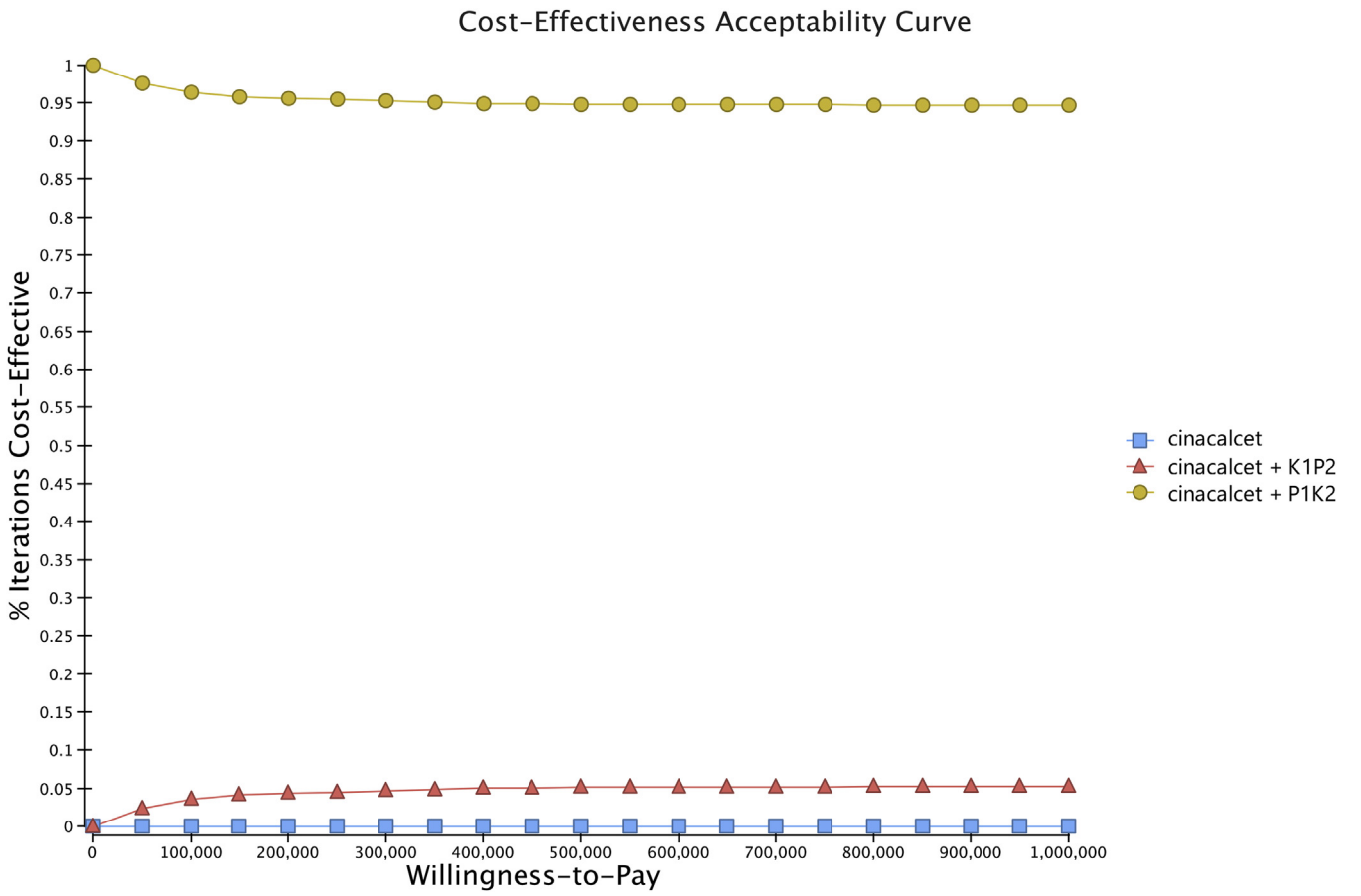

Fig 3. The cost-effectiveness acceptability curve. The PTX before KTxp with cinacalcet (P1K2) strategy remained dominant compared with PTX after KTxp with cinacalcet (K1P2) and cinacalcet alone with KTxp, as demonstrated by the fact that the curve plateaus as willingness-to-pay increases.

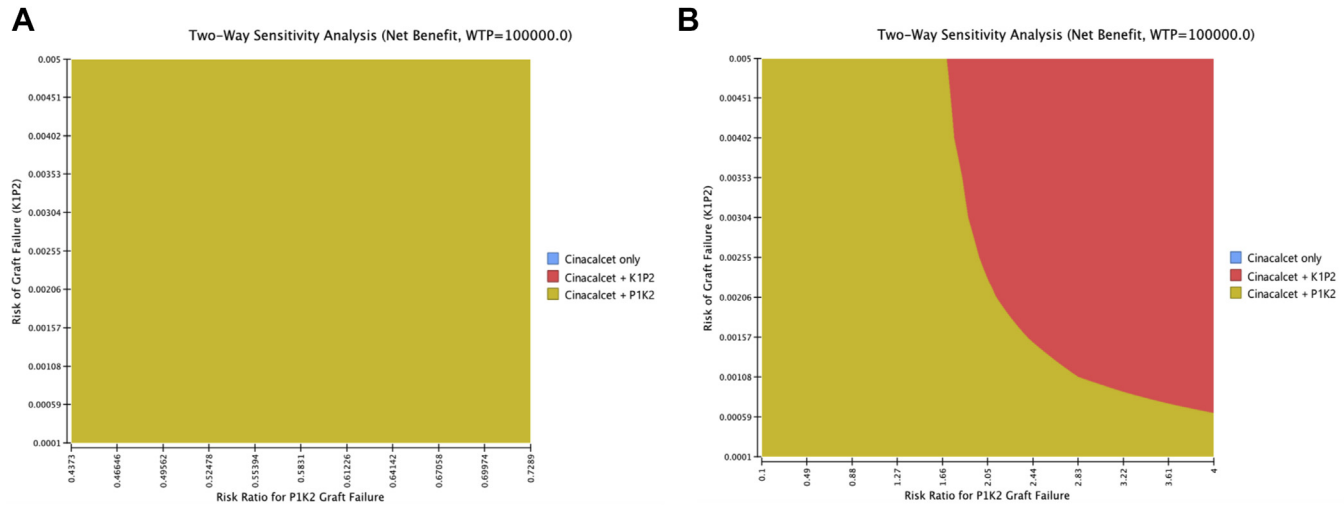

Fig 4. A two-way sensitivity analysis of the risk of graft failure for the K1P2 strategy versus the risk ratio of graft failure for the P1K2 strategy at a WTP of 100,000. (*A*) The P1K2 strategy remained completely dominant when the risk ratio of graft failure for the P1K2 strategy extended over a range of ±25%. (*B*) Demonstrates when the K1P2 strategy becomes cost effective.

and more cost-effective for ESRD patients on dialysis with severe hyperparathyroidism compared to lifetime treatment with cinacalcet alone. Specifically, the authors concluded that unless the patient was anticipated to die or undergo a KTxp within 7 months, PTX was the most cost-effective strategy. Of note, the authors defined severe HPT as patients with a serum PTH >300 pg/mL, which is in line with our definition of 3HPT.[14] When comparing treatment with PTX versus cinacalcet among kidney transplant patients with 3HPT, both Cruzado et al and Lou et al found that PTX was not only safe for patients with 3HPT, but it was also associated with a greater cure rate and was more effective at resolving hypercalcemia.[3,24]

As far as timing of PTX, our study found PTX before KTxp was associated with less cost, a greater overall life expectancy, and a greater quality of life compared with PTX after KTxp. This result is largely due to the impact that 3HPT can have on graft function among KTxp patients. If there is an increased risk of graft loss post-KTxp, the patient returns to an ESRD state, which incurs cost and disutility.[5] We found that the graft failure rates from our model were more conservative for the P1K2 and K1P2 strategies in comparison to the graft failure rates for a 55- to 59-year-old patient undergoing a deceased donor renal transplantation reported in the 2019 United States Renal Data System (Table III). Consequently, the differences between the P1K2 and K1P2 strategies may be even more pronounced than what our model suggests. In 2017, Callender et al evaluated the risk of graft failure among hyperparathyroid patients with ESRD who underwent a PTX before KTxp (the P1K2 strategy) versus those who were treated with KTxp and cinacalcet alone. They found that the risk of graft failure among P1K2 patients was less compared with KTxp patients with cinacalcet; however, there was no difference in delayed graft function, serum calcium levels, or eGFR between the 2 groups. Thus, this group recommended that if pre KTxp PTH levels are >6 times normal, PTX should be considered before KTxp.[6] These results support the 2017 KDIGO guidelines that recommend PTX for patients with hyperparathyroidism associated with ESRD, defined as PTH levels greater than 2 to 9 times the upper limit of normal despite maximum medical therapy with vitamin D analogs and calcitriol.[1] Furthermore, in 2019 Littbarski et al[5] performed a retrospective analysis of patients with severe 2HPT (also referred to as 3HPT) and kidney transplant to determine the greatest risk factors associated with graft failure. The authors determined that having a PTX after a KTxp was an independent risk factor for graft failure 1 year after transplantation.

In contrast, a multicenter, retrospective analysis published in 2016 aimed to evaluate the difference in renal function between 2 different treatment pathways: PTX before KTxp (P1K2) and PTX after KTxp (K1P2). They found that 5 years after KTxp, the eGFR was similar between the 2 groups and that timing of PTX was not correlated with graft dysfunction over time[3]; the retrospective nature of this study limited the ability to discern the indications for PTX. Therefore, it is possible that patients who were included in the P1K2 strategy were sicker and not expected to undergo a KTxp or they had more severe hyperparathyroidism compared with those in the K1P2 strategy. Additionally, patients who developed primary graft nonfunction (10% in the P1K2 group and 17.9% in the K1P2 group) were excluded from additional analysis, which may have minimized the potential immediate adverse effects of 3HPT on graft function. These discrepancies could have skewed the rates of graft failure in favor of the K1P2 strategy, which would have led to a nonstatistically significant difference in the graft failure rate compared with the P1K2 strategy.

To determine the rate of graft failure among patients who had a PTX before KTxp, we extrapolated from the Littbarski study, which is the most recent study that directly compares the odds of graft failure between patients undergoing a KTxp before and after PTX. According to our sensitivity analysis, our model was robust to variations in rates of post-KTxp graft failure. In order for the K1P2 strategy to become cost-effective, the rate of graft failure in the K1P2 strategy would have to decrease by 5 times from 0.25% to 0.045%.[5] Conversely, in the P1K2 strategy, the PTX would have to be unsuccessful, and the rate of graft failure in the P1K2 strategy would have to double from 0.15% to 0.37% for the K1P2 strategy to be cost-effective.[5,10]

In addition to the decreased rate of graft dysfunction associated with the P1K2 strategy, other health benefits have been described that encourage earlier operative intervention among patients with 3HPT. Patients with 3HPT who undergo PTX have lesser rates of all-cause mortality and cardiovascular mortality compared with those patients treated medically.[8] Similarly, our study demonstrated that patients who undergo early PTX before KTxp have a greater overall life expectancy and greater QALYs compared with the patients undergoing a delayed PTX after KTxp or those who are only treated medically for their 3HPT. Furthermore, PTX is associated with decreased fractures and improved bone health among dialysis patients. For example, Abdelhadi et al showed that PTX among patients on dialysis increased bone mineral density by 7% to 23% within 6 months, compared with a 1% to 8% increase among patients who underwent a PTX after a KTxp. The lesser rate of bone recovery after PTX among KTxp patients could potentially be due to immunosuppression.[23,25]

Our decision model has several important limitations. We made the assumption that all patients with 3HPT pre-KTxp were able to undergo PTX, whereas in reality, these patients may have other medical factors that put them at an unacceptable preoperative risk. Furthermore, we did not account for patients with ectopic parathyroid glands that may warrant a more extensive operation for resection. These assumptions would favor the P1K2 with cinacalcet strategy compared with the others and therefore we tested the validity of these assumptions using the threshold and probabilistic sensitivity analyses. Additionally, our estimated costs, relative risks, and rates of mortality were obtained from the literature, which varies by study design, geographic population, and date of publication. The goal of our sensitivity analysis was to challenge these values across a wide range in order to minimize this limitation. Despite these limitations, we believe that the results of our study provide strong evidence that PTX before KTxp is the most cost-effective treatment strategy for addressing this disease in this patient population.

In conclusion, our results demonstrate that once patients progress from chronic 2HPT to an unregulated 3HPT marked by PTH levels >2 to 9 times the upper limit of normal with or without hypercalcemia, PTX is superior to treatment with cinacalcet alone. Consequently, when providers reach the point of initiating therapy with cinacalcet, either due to markedly increased serum PTH or calcium levels, the providers should also consider referring the patient to an endocrine surgeon for PTX. Furthermore, performing a PTX before a KTxp is more cost-effective compared with performing PTX after a KTxp. Thus, providers should consider earlier PTX for patients with 3HPT prior to KTxp.

Conflict of interest/Disclosure

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Funding/Support

The authors have indicated that they have no funding regarding the content of this article.

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