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When There Will Never be a Randomized Controlled Trial

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Abstract

There are many unanswered questions about how to best manage secondary hyperparathyroidism and associated alterations in mineral metabolism in patients with end-stage renal disease. We provide editorial commentary on an observational study published in this edition of *Kidney International* that presents interesting new insights into the longstanding controversy related to the impact of parathyroidectomy on survival of hemodialysis patients.

Keywords

parathyroidectomy; parathyroid hormone; end-stage renal disease; hemodialysis; mineral metabolism; mortality

Treatment of secondary hyperparathyroidism in patients with end-stage renal disease is an area rife with controversy and therapeutic uncertainty. For an area that so deeply permeates daily dialysis practice and is so strongly linked to survival on dialysis (1), the clinical conundrums for which randomized trials are needed far outnumber the few trials that have been performed (2, 3). For many questions related to mineral metabolism, we remain optimistic that trials may eventually come. But in the case of surgical parathyroidectomy for severe secondary hyperparathyroidism, it is unlikely that there ever will be a randomized controlled trial. To address the questions of whether, when and in whom parathyroidectomy should be considered, we are left to resort to observational studies with all their intrinsic limitations.

Komaba *et al* dive into this evidence gap in this issue of *Kidney International* (4). They tested the hypothesis that parathyroidectomy is associated with improved survival of hemodialysis patients with severe secondary hyperparathyroidism. Using 2004–2005 data

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from a national dialysis registry in Japan, the authors studied the association of facility-reported parathyroid hormone (PTH) levels with survival in a cohort of over 100,000 patients, stratified by prior history of parathyroidectomy. To further test the impact of parathyroidectomy on survival, the investigators limited the group of non-parathyroidectomy control patients to those who had a potential indication for parathyroidectomy by requiring a PTH >500 mg/dl at the start of the observation period. In each of these analyses, the authors report that the 6,600 patients who had previously undergone parathyroidectomy had significantly lower risks of all-cause and cardiovascular mortality during the fixed 1-year observation period.

Not surprisingly, there were numerous differences in clinical characteristics and laboratory parameters between patients who had previously undergone parathyroidectomy and those who had not. To reduce these potential sources of confounding, the authors calculated a propensity score of having previously undergone parathyroidectomy based on clinical characteristics recorded during the 2004 – 2005 study period. They used the propensity score to one-to-one match parathyroidectomy and non-parathyroidectomy patients. The survival benefit of parathyroidectomy persisted in this analysis of approximately 4,400 patient pairs, and also in several other sensitivity analyses.

Compared to prior studies that investigated the impact of parathyroidectomy on survival, this study has several strengths. Most notably, the study sample was large, nationally representative, and the authors had access to certain laboratory data that were unavailable in previous studies. However, several limitations related to the study's unorthodox design must be considered when interpreting the results.

To minimize potential sources of bias, observational studies of the impact of specific treatments should be designed to most closely approximate how the corresponding randomized controlled trial would be designed. In an ideal trial of parathyroidectomy for severe hyperparathyroidism, patients would be monitored on dialysis until they first developed evidence of refractory secondary hyperparathyroidism. At that time, patients would be randomized to surgical parathyroidectomy or to continued medical management, and both groups would be monitored prospectively for outcomes (Figure A). In the ideal observational analog of such a trial, clinical data would be collected during the pre-parathyroidectomy period; the start of survival follow-up would be linked to when the indication for parathyroidectomy was first established; and all subsequent deaths would be captured. In contrast, the current study was limited by only having data between 2004 and 2005. As a result, patients were not under observation in the study at the time when the indication for parathyroidectomy was established, and deaths that occurred between parathyroidectomy and the start of the study's observation period were not accounted (Figure B). This source of bias favors the parathyroidectomy group because of the relatively high mortality rates during the immediate post-parathyroidectomy period (5, 6). In addition, the potential indication for parathyroidectomy of PTH >500 pg/ml that was used to restrict the control group was defined at the start of the study period leading to potentially misalignment of follow-up time across the two groups (Figure B). Although it is hard to know in which direction this particular bias cuts, it complicates our interpretation of the results.

Like other observational studies of clinical interventions, confounding by indication is also a nemesis of the current report. In this form of confounding, the reasons why certain patients are chosen to or are able to receive a specific treatment identify them as having a higher likelihood of prolonged survival than patients who are left untreated. The treatment may actually be beneficial, but it is also possible that simply being eligible to be treated artificially generates a false benefit in an observational study. Confounding by indication is an important limitation when the treatment in question is a medication, but it may be further accentuated when the treatment is surgical, as in the case of parathyroidectomy for severe secondary hyperparathyroidism. In this case, when nephrologists refer patients for parathyroidectomy, they have often already concluded that the operative risks are surmountable and the net calculus of costs and benefits favor proceeding. Contrast that with patients with similarly severe secondary hyperparathyroidism who nephrologists might refer if not for the patients' poor general health status and the sense that the surgical risks outweigh the potential benefits.

The only definitive strategy to eliminate confounding by indication is randomization. When randomization is not possible, investigators may use other strategies such as propensity scores to balance characteristics across treatment groups. Propensity scores use observed variables to predict the likelihood that each patient would receive the therapy in question. Matching pairs of patients with identical propensity scores in whom the investigational treatment was given to one and withheld in the other attempts to mimic the balancing effects of randomization. While propensity score matching is a methodologically sound approach, how Komaba *et al* used it was atypical. Ideally, the propensity score would have been used to match patients on the basis of *pre-treatment* factors that influenced their likelihood of undergoing parathyroidectomy, but the pre-treatment factors were not available to the investigators in this study. Instead, they used clinical characteristics that were assessed at the start of the study period to "predict" the likelihood of having previously undergone parathyroidectomy, often long after it was already performed (Figure B). Since the authors justifiably excluded post-treatment PTH, calcium and phosphate levels from the propensity score because they are directly affected by parathyroidectomy, mineral metabolism parameters, which are arguably the most important clinical predictors of undergoing parathyroidectomy, did not even enter into the propensity score model.

Despite the methodological challenges, Komaba *et al*, report several findings of interest to the field. They confirm prior findings of a J-shaped relationship between PTH and survival (7, 8), and extend these results in an important way. At both extremes, low and high PTH were each associated with significantly higher risk of mortality than midrange levels, but Komaba *et al* observed this trend only among patients who had not undergone parathyroidectomy. In contrast, among patients who had previously undergone parathyroidectomy, the lowest PTH levels were associated with the best clinical outcomes. Similar to this report, recent data from the Dialysis Outcomes and Practice Patterns Study demonstrated that the higher risk of mortality associated with very low PTH was most evident among patients who had not received any treatment for secondary hyperparathyroidism (9). These important findings emphasize the potential pitfalls of developing clinical guidelines that advocate for achieving biochemical targets for individual parameters of mineral metabolism without considering the context of current and past

treatments. They also illustrate the critical need for more information on the efficacy of treatment of secondary hyperparathyroidism rather than target PTH levels.

As a corollary, the finding that both high and low PTH can be associated with higher risk of mortality indicates that the absolute PTH level does not clearly segregate with risk of death. This may suggest that PTH is not the causal mediator of mortality, but instead, is a broad indicator of other critical derangements in mineral metabolism that directly confer risk. If definitive treatment of secondary hyperparathyroidism with surgical parathyroidectomy does improve survival, as suggested by Komaba *et al*, this could be mediated by changes in several biochemical parameters that are impacted by parathyroidectomy, including phosphate, calcium, fibroblast growth factor 23 and possibly, other unknown factors. Viewed in this light, the current study is broadly supportive of targeting mineral metabolism to reduce mortality in patients undergoing hemodialysis, and it should encourage our ongoing quest to identify the most effective treatments.

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References

1. Covic A, Kothawala P, Bernal M, et al. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. *Nephrol Dial Transplant*. 2009; 24(5):1506–23. [PubMed: 19001560]
2. The EVOLVE Trial Investigators. Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis. *N Engl J Med*. 2012; 367(26):2482–94. [PubMed: 23121374]
3. Suki W, Zabaneh R, Cangiano J, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int*. 2007; 72(9):1130–7. [PubMed: 17728707]
4. Komaba H, Taniguchi M, Wada A, et al. Parathyroidectomy and survival among hemodialysis patients with secondary hyperparathyroidism: results from a nationwide registry in Japan. *Kidney Int*. 2015 Epub ahead of print.
5. Ishani A, Liu J, Wetmore J, et al. Clinical outcomes after parathyroidectomy in a nationwide cohort of patients on hemodialysis. *Clin J Am Soc Nephrol*. 2015; 10(1):90–7. [PubMed: 25516915]
6. Kestenbaum B, Andress DL, Schwartz SM, et al. Survival following parathyroidectomy among United States dialysis patients. *Kidney Int*. 2004; 66(5):2010–6. [PubMed: 15496173]
7. Floege J, Kim J, Ireland E, et al. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. *Nephrol Dial Transplant*. 2011; 26(6):1948–55. [PubMed: 20466670]
8. Dukkipati R, Kovesdy C, Colman S, et al. Association of relatively low serum parathyroid hormone with malnutrition-inflammation complex and survival in maintenance hemodialysis patients. *J Ren Nutr*. 2010; 20(4):243–54. [PubMed: 20199875]
9. Tentori F, Wang M, Bieber BA, et al. Recent Changes in Therapeutic Approaches and Association with Outcomes among Patients with Secondary Hyperparathyroidism on Chronic Hemodialysis: The DOPPS Study. *Clin J Am Soc Nephrol*. 2015; 10(1):98–109. [PubMed: 25516917]

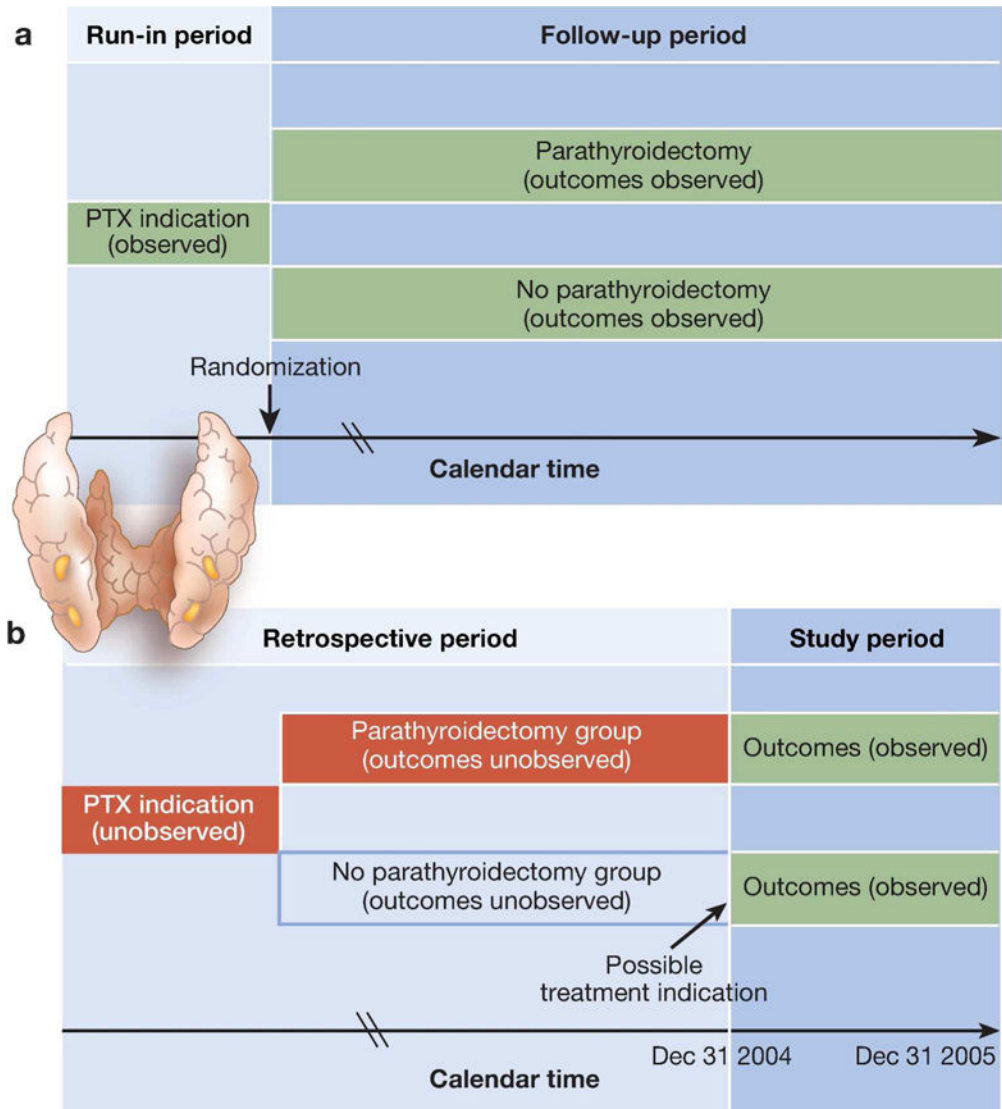


Figure. Schematic Representation of the Study Design and its Potential Biases in Contrast to the Optimal Randomized Controlled Trial

Figure A depicts the optimal randomized controlled trial that would prospectively assess patients from initiation of dialysis until they developed an indication for parathyroidectomy, namely refractory secondary hyperparathyroidism. At that point, patients would be randomized to surgical parathyroidectomy or continued medical management with ongoing prospective follow-up. Figure B depicts the design of the current study, which examined clinical data and survival between December 31, 2004 and December 31, 2005, except for history of parathyroidectomy, which could have occurred at any earlier time. The investigators compared survival of patients who had previously undergone parathyroidectomy to patients who had a potential indication for parathyroidectomy (PTH>500 pg/ml) at the start of the study period but who had not previously undergone parathyroidectomy. This study design introduces several limitations that complicate interpretation. Since parathyroidectomy patients had to survive until December 31, 2004 to enter the study period, any deaths that occurred between parathyroidectomy and the start of

the study period were not observed. Also, patients' clinical characteristics at the time they developed their indication for parathyroidectomy were not observed in the treatment group, making it difficult to ensure that treated and untreated groups had adequately matched characteristics prior to parathyroidectomy. Finally, since the study pegged baseline clinical characteristics and survival follow-up time to a fixed calendar period rather than the timeframe of individual patients' dialysis experience, follow-up time was misaligned.

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