IN FOCUS

Parathyroidectomy and patient survival in CKD patients

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Secondary hyperparathyroidism (SHP) in patients with chronic kidney disease (CKD) is recognized as a key player in most of the adverse outcomes observed in this clinical setting [1, 2]. Until not much later than a decade ago, the therapy available for SHP control was limited and of relatively low efficacy, so that the indication to parathyroidectomy (PTX) remained high up to the beginning of the present century [3, 4]. More recently, an astonishing increase in new medical tools available to control SHP has translated into an improved control of biochemical parameters, with a progressive reduction in the use of PTX [5]. Despite a better biochemical control of SHP, no evidence has been produced of a positive impact of any of these new treatments on mortality [6, 7]. In view of the fact that the cost of these new medical therapies is far higher than PTX [8, 9], the critical question of which of the two strategies, the medical or the surgical therapeutic approach, is more cost effective remains of critical relevance. That being said, any new scientifically appropriate data that could add information in this field are welcome.

In this issue of NDT, Ivarsson et al. [10] analysed the Swedish Renal Registry to explore the impact of PTX on

CONFLICT OF INTEREST STATEMENT

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(See related article by Fishbane et al. Ferric pyrophosphate citrate (Triferic™) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients. Nephrol Dial Transplant 2015; 30: 2019–2026.)

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mortality both in patients on dialysis treatment and in those who received a renal transplant over 19 years. The authors identified 579 PTX patients who were compared with 1970 non-PTX patients, matched for gender, age, cause of end-stage renal disease and for having, or not, a functioning renal graft at the date \((d)\) when PTX was performed, with \(d\) representing the starting point for measuring the number of observed deaths in both PTX and non-PTX groups. The authors observed a significantly lower hazard ratio (HR) for death in PTX patients compared with non-PTX patients, which remained lower even after correcting for comorbidities, time on renal replacement therapy before \(d\) and time with a functioning graft before and after \(d\). Interestingly, when the risk was assessed after stratification of the patients according to the renal replacement therapy modality, a significant difference in HR for death was observed only in patients on dialysis treatment, but not in transplanted patients. These results are consistent with most \([4, 11–13]\), though not all \([14]\), previous studies and have the specific strength of being based on a large national registry with a long follow-up.

However, we still need to consider the number of potential critical points common, in part, to all the studies dealing with the issue of PTX in CKD patients, the most relevant of which I will briefly address in the following paragraphs.

One of the major problems encountered when comparing the outcomes of PTX cohorts is the definition of the criteria on which the indication to the intervention is based. In many of these studies, the criteria are not specified at all, while in others, they are quite variable and are different based on (i) the level of PTH per se, with different cut-off values from one study to another (>800, >1200, 10-fold the upper normal limit, etc.); (ii) PTH levels associated with higher calcium and/or phosphorus serum levels (again with highly variable ranges of values) and (iii) high PTH levels associated with bone disease \([4, 10–14]\).

Furthermore, only occasionally, the therapy on which these values are observed is specified. It is counterintuitive that this missing information, in addition to the high variability of the biochemical indications, can heavily affect the results of the various studies. In fact, it is easy to understand that extremely different degrees of SHP, with possibly quite different mortality risks, could have been inappropriately categorized in the different studies as deserving the same therapy (PTX).

The types of surgical intervention to perform PTX reported in the literature are manifold: (i) partial (1–3 glands) PTX, (ii) subtotal PTX (three complete glands plus one-half of the fourth, usually the smallest one), (iii) total PTX with autotransplantation of the smallest gland or of a piece of it into the forearm or anterior tibial muscle or subcutaneously and (iv) total PTX without autotransplantation \([15–18]\).

Furthermore, any of the above interventions can be associated, or not, with total thymectomy. As a consequence, all these interventions, though to a variable extent, can result in consistently different outcomes, since they can be followed by a hypoparathyroid status, a well-controlled persistent mild SHP or by the recurrence of a severe form of SHP, immediately after or at variable times after PTX \([15, 19]\). It goes without saying that the different medical or surgical needs and the clinical implications associated with the above outcomes can consistently and variably influence the morbidity and mortality of the PTX patients. In fact, some studies do not report at all which type of PTX was performed and those that do only occasionally report on the influence of the type of PTX performed and on its surgical and medical outcome in relation to the possibly different clinical outcomes of the patients. If the more recently proposed surgical modalities of total PTX, associated to subcutaneous infusion of a limited amount of parathyroid tissue, might help in obtaining a much more standardized result deserves more in depth examination \([20, 21]\).

The main critical and unsolved question is which should be the ideal control group for the PTX cohorts.

In fact, matching only for age, dialysis vintage and comorbidities does not take in the most important information. First of all, it would be essential to know how many matched patients could have had an indication to PTX which may not have been performed due to clinical reasons, which are not necessarily captured by multivariate analysis. This ‘occult’ clinical bias might inappropriately induce a false-positive effect on survival in the PTX cohort, given the higher morbidity of the patients excluded from PTX. If instead an indicated PTX was not performed due to the patient’s refusal, this might imply that these non-PTX patients might be burdened by an uncontrolled severe SHP, with an expected negative impact on the survival.

On the other hand, if only patients without or with a mild degree SHP are included in the control group, we could also bias the comparison, given that patients with more severe SHP are often younger, less likely to be diabetic, malnourished and inflamed.

The introduction of cinacalcet in the clinical practice about a decade ago increased the expectation for a ‘chemical’ PTX as a definitive substitute of the surgical intervention \([22]\). In fact, though there was a significant reduction in the use of PTX, it became evident over time that PTX is still necessary in a consistent number of patients, due to the drug-related adverse effects and/or intolerance, and in some cases also to the ineffectiveness of the drug in the control of severe SHP. In addition, as previously mentioned, the cumulative cost of the cinacalcet-based medical therapy is greater than the cost of PTX after ∼7 months of treatment \([8]\). On the other hand, we are also aware that PTX cannot be easily performed in all patients, in particular in the elderly, high-morbidity patients or in patients already submitted to a previous PTX \([23]\). However, even if we exclude patients who are not eligible for PTX or patients not tolerant of or unresponsive to cinacalcet, it is still a significant number of patients who could indifferentely benefit by each of the two options. So, the demonstration of the equivalence or not between the two options regarding the main clinical outcome (mortality) is of outstanding relevance.

In conclusion, though it is important to collect new data supporting the safety of PTX and suggesting a clinical advantage for PTX patients, a more definite opinion could be reached only after a multi-centre trial specifically directed to explore this issue.

To perform such a ‘quasi’-ideal trial, one should (i) strictly define the criteria for PTX indication; (ii) choose the surgical technique that ensures a higher probability of inducing a
good control of SHP; (iii) identify patients who have no contra-

indication either to the surgical (PTX) or maximal medical

therapy (cinacalcet and/or vitamin D analogues); (iv) collect

their consent to be treated with either of the two (surgical or

medical) therapies; (v) randomize these patients to one of the

two treatments; (vi) follow them for a long enough time to
gather information on the clinical outcome, therapy failure
and adverse events and (vii) collect complete information on
the concomitant SHP-directed and non-SHP-directed therapies.

But, can we expect that such a trial will be realized? Hoping
you do not sin!

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Ivarsson et al. The effect of parathyroi-
dectomy on patient survival in secondary hyperparathyroidism.

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