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Original Article

Parathyroidectomy as a therapeutic tool for targeting the recommended NKF-K/DOQI^{TM} ranges for serum calcium, phosphate and parathyroid hormone in dialysis patients

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Abstract

Background. The recommended NKF-K/DOQI'99 ranges for Ca, P and PTH in dialysis seem advisable also for patients previously submitted to parathyroidectomy; however no paper addresses, specifically in this condition, to what extent optimal values are targeted in the short and long term after surgery.
Methods. We checked serum Ca, P and PTH basally and after 1 month and 1, 3 and 5 years since surgery, in 77 dialysis subjects who received parathyroidectomy in our hospital.
Results. Immediately after surgery all biochemical parameters dropped, but afterwards Ca showed a tendency to increase progressively in the long term ($p < .0006$), P increased mostly within one year ($p < .01$), and PTH increased similarly to Ca ($p < .003$), but with mean values always in the lower than desired range. The estimated percentage of patients at target during the follow-up was maximal for P (values between 65 and 76%), lower for Ca (zenith of 43% after 1 month but declining down to 14% after 5 years) and minimal for PTH (invariably <10%). Persistence within the ranges (at least on two consecutive checks) was 21% after one month for Ca, with a tendency to reduction; 41% for P, with a tendency to average roughly 30%, and practically zero for PTH. Neither type of surgery (total or subtotal) nor vitamin D therapy were associated with the low values of PTH observed.
Conclusions. We conclude that parathyroid surgery does not represent an optimal therapeutic tool for targeting the recommended ranges for Ca, P and PTH. In particular, too low PTH values are frequently obtained, whose clinical effects deserve further studies. The possibility of a time dependent risk for recurrence is confirmed.

Keywords: NKF-K/DOQI guidelines; parathyroid hormone; parathytroidectomy; secondary hyperparathyroidism

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Introduction

The recently introduced NKF-K/DOQI^{TM} guidelines, by recommending much more restricted ranges for serum levels of Ca, P and parathyroid hormone (PTH) [1], have definitely affected the management of mineral metabolism in uraemic patients. In fact, numerous observational studies have underlined both the very high prevalence of cases not fulfilling the newly suggested intervals [2] and the very low prevalence of patients targeting altogether the three recommended ranges [3]. As a result, many of the clinical trials employing new drugs in this field (like cinacalcet, paricalcitol or lanthanum) now claim the increased probability of targeting one or more of these biochemical end-points during treatment [4–6].

Nonetheless, despite these new drugs, several patients continue and will predictably continue to suffer from unresponsive secondary hyperparathyroidism requiring surgery, which, similar to other therapeutic tools, is expected to facilitate the accomplishment of these recently introduced targets. Actually, data in the literature testify the efficacy of surgery both in the short [7–11] and long term [7,9,12,13]; however, until recently the authors have empirically selected different PTH thresholds to classify failure (intended as persistence or recurrence of the disease) or success (intended as significant reduction of PTH levels) [7,9,11]. These threshold levels vary between 'normal reference' [8,11] and 200 pg/ml [9], while, to our knowledge, no published paper examines to what extent patients submitted to parathyroidectomy are allowed to accomplish the newly recommended NKF-K/DOQI^{TM} ranges not only for PTH but also for serum Ca and P, in the short- and long-term interval. This point is particularly intriguing since we are actually concerned not only with severe hyperparathyroidism, but also with the opposite situation, hypoparathyroidism.

Accordingly, in our study we aimed at evaluating whether patients submitted to parathyroidectomy actually target optimal serum levels of PTH, Ca and P in the short and long term.

Methods

Patients and methodology

Between 2000 and 2005 a total of 77 dialysis patients, referred to our hospital from several dialysis units, received a parathyroid surgery. Clinical, biochemical and radiological signs of severe parathyroid over function were evident in each patient, and in particular: 38 had extremely elevated PTH levels (>800 pg/ml), increased alkaline phosphatase and unsuccessful medical treatment attempts with active vitamin D; 18 had severe persistent hypercalcaemia and hyperphosphataemia precluding vitamin D administration; 16 had ultrasonographic evidence of one or more significantly enlarged parathyroid glands (>1 cm^3) and 5 suffered also from intractable pruritus.

Surgical exploration of the neck involved identification of all the parathyroid glands and of the thyrothymic ligament in every patient, followed by their excision in 69. In fact in 8 patients 5/6th of a well-vascularized and morphologically conserved gland was left in place, while in 33 patients 20 pieces of tissue obtained from the best morphologically preserved gland and ranging from 1 to 2 mm^3 were implanted into the brachioradialis muscle of the arm opposite to that of the arterio-venous fistula. All removed specimens were microscopically examined to confirm the diagnosis. Therefore, according to clinical criteria, the surgical techniques employed in this study can be divided into two types: total (all isolated glands, in 36 patients) and subtotal, either with removal of three glands and five-sixths of the fourth (8 patients) or total plus forearm auto-transplantation (33 patients). After surgery patients were summoned on a regular basis in order to check the biochemical and clinical outcomes. Our schedule consisted of central biochemical assays and records of current therapies 1 month and 1, 3 and 5 years after surgery.

Daily adjustments in the therapy of secondary hyperparathyroidism, according to the levels of Ca, P and PTH, were left to the single nephrologist responsible for each patient and relied on the administration of vitamin D (as oral or i.v. calcitriol) and of phosphate binders (such as sevelamer, calcium carbonate or acetate). A minority of patients received aluminium hydroxide, but none was taking calcimimetics or vitamin D analogs.

Assays

PTH was assayed with a commercial kit based on an IRMA method employing a double antibody against the intact human molecule (DiaSorin, Stillwater, MN, USA); our normal values range within 10–55 pg/ml, with intra- and inter-assay variations of 6.5 and 9.8%, respectively. Serum levels of Ca, P and albumin (used to correct Ca values) were assayed by standard, colorimetric, automated techniques, employing the cresolphthalein complexone, the ammonium molybdate and the bromcresol purple methods, respectively.

Statistics

Data analysis was performed using R software (R Foundation for Statistical Computing, Vien, Austria, ISBN 3-900051-07-0). Besides standard descriptive statistics and graphs for longitudinal data, for each of the three responses (Ca, P and PTH) we fit a linear mixed-effects model which includes fixed-effects parameters for the covariates and a random intercept to take into account the dependence over time of the observations from the same subject. The covariates used were: time of observation, dialysis duration, vitamin D therapy, type of surgery, reason to loss at follow-up, age, sex and baseline serum levels. The final model was chosen using a stepwise variable selection algorithm. In practice only the baseline serum levels and time were finally selected for all the three responses. When needed, the mixed-effects model was also used to estimate the responses of subjects with unavailable follow-up data. Further, a multiple events per subjects Cox model was estimated to evaluate, for each variable, the probability of persisting, during the follow-up, within the recommended NKF-K/DOQI™ ranges. For each subject an event is defined as being observed outside the range, and we recorded the time between events. That is, there is persistence whenever the subject is observed within for at least two consecutive follow-up visits; there is censoring whenever at the end of follow-up the subject is inside the ranges. A 95% confidence interval for each estimated probability was obtained. Tests on the significance of the parameters of the models were conducted at level alpha = 5%. Data are expressed as M ± SD.

Results

Clinical and biochemical data pertinent to the 77 patients (38 M; 29 F; aged 54 ± 12 years) at the time of surgery are detailed in Table 1. The presence of high PTH values (1074 ± 448 pg/ml) is evident, together with similarly increased mean values of Ca (10.9 ± 0.9 mg/dl) and P (6.2 ± 1.5 mg/dl).

So far, follow-up data are available for all patients after 1 month, while those checked after 1, 3 and 5 years are 72, 47 and 27, respectively. In fact some patients have not yet reached all the temporal end-points ($n = 24$), while others have been censored due to renal transplantation ($n = 5$) or death ($n = 9$). Twelve cases are considered lost to the follow-up for unknown reasons.

Figure 1A, showing the time-course of Ca following surgery, indicates a reduction of values and also the occurrence of wide fluctuations above, within or below the recommended range. The box-plot graph (Figure 1B) better describes the occurrence of a progressive increment of

Table 1. Clinical and biochemical characteristics of the population under study

Patients, no	77	Ranges
Sex	38 M/29 F	
Age (years)	54 ± 12	23–72
Dialysis vintage (years)	7.7 ± 4	2–20
Serum PTH (pg/ml)	1074 ± 448	338–2170
Serum albumin (g/dl)	3.7 ± 0.5	2.7–5.2
Serum calcium (mg/dl)	10.9 ± 0.9	8.9–12.9
Serum phosphorus (mg/dl)	6.2 ± 1.5	2.7–10.9

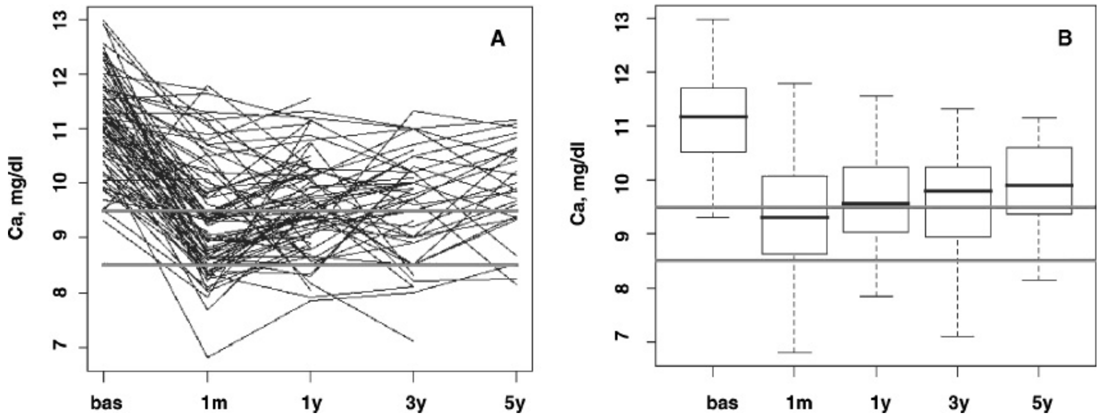

Fig. 1. Time-course of individual values (**A**) and box-plot graph (**B**) of serum calcium following parathyroid surgery.

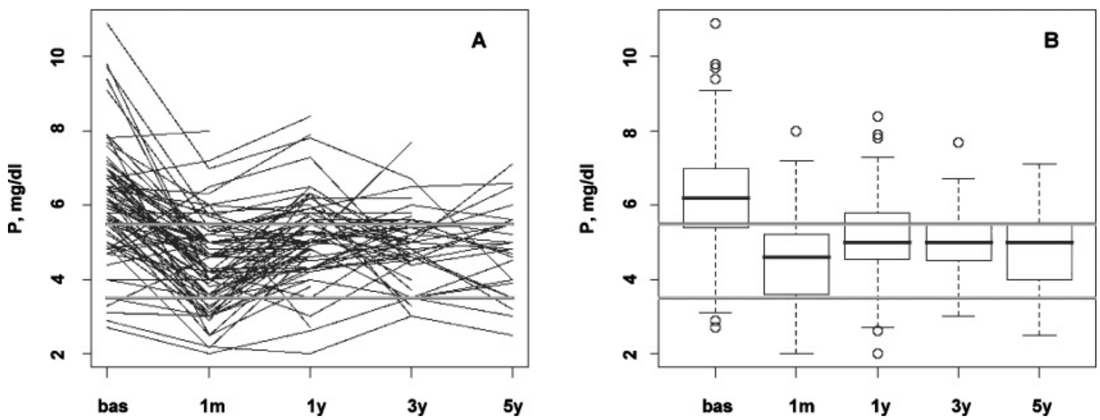

Fig. 2. Time-course of individual values (**A**) and box-plot graph (**B**) of serum phosphate following parathyroid surgery.

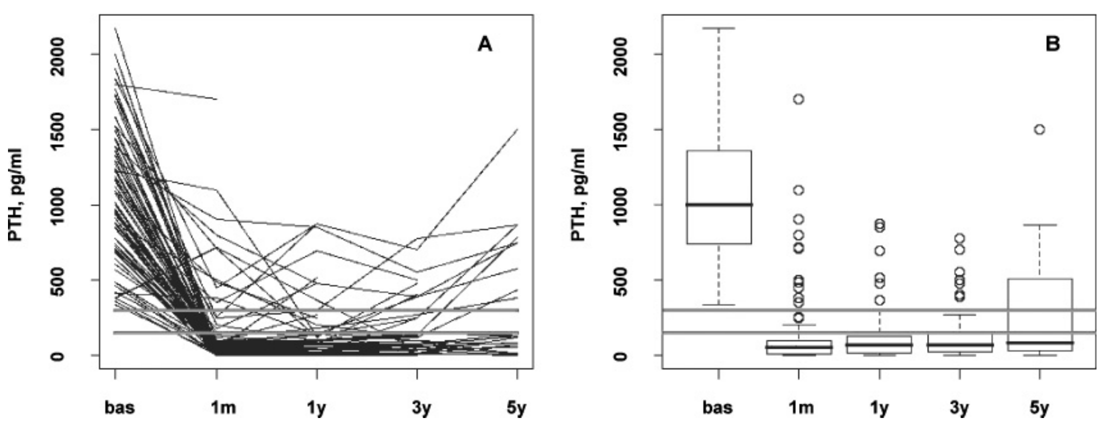

Fig. 3. Time-course of individual values (**A**) and box-plot graph (**B**) of serum parathyroid hormone following parathyroid surgery.

values during the follow-up and in fact the linear mixed-effects model estimated a positive role for time ($P < 0.0006$). In contrast, covariates like sex, age and dialysis duration showed no significant association.

As for serum P, similar to Ca, a drop in values was observed associated with an evident fluctuation after surgery (Figure 2A). The box-plot graph (Figure 2B) evidentiates, after a drop, an increment occurring mainly within the first year, followed by a substantial stability. Actually, the linear mixed-effects model estimated a positive association between serum phosphate and time since surgery ($P < 0.01$) and no role for covariates like age, sex and dialysis duration.

Finally, Figure 3A, showing the time-course of PTH values, indicates the impressive effect of surgery, but also the quite low number of cases targeting the recommended 150–300 pg/ml interval. The box-plot graph (Figure 3B)

Table 2. Estimated percentage of cases targeting the recommended ranges for Ca, P and PTH in our population, basally and during follow-up. Values from the DOPPS study are also shown, for comparison

	DOPPS	PTX Basal	1 month	1 year	3 year	5 year
Ca	40.5	3.9	43	36.8	25	14
P	40.9	23	65	65	74	76
PTH	22.2	0	6.5	9.1	9.1	7.8

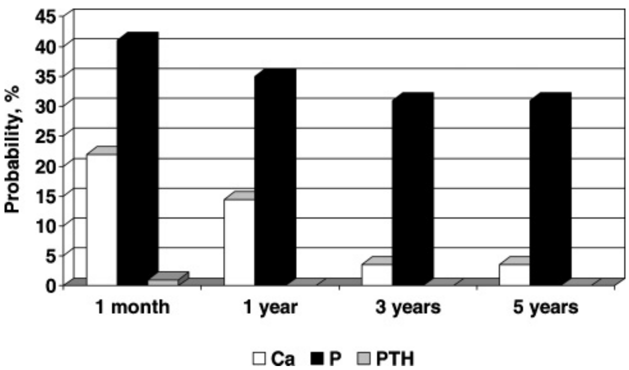

Fig. 4. Probability of persisting within the recommended ranges for Ca, P and PTH following parathyroidectomy.

suggests an increment of PTH values in the long term, an effect confirmed by the linear mixed-effects model, indicating time since surgery as a significant factor for PTH increment ($P < 0.003$), again with no role for sex, age and dialysis duration.

We then applied the mixed-effects model to estimate the percentage of our patients targeting the recommended NKF/K-DOQI^{TM} ranges basally and during follow-up (Table 2); as a comparison, in the table, we also show the data from a standard dialysis population, like that of the Dialysis Outcomes and Practice Patterns Study (DOPPS)[2]. The most striking improvement after surgery is obtained with serum phosphate which, from a low pre-surgery 23%, increases to between 65 and 76% during follow-up. An improvement is also observed for serum Ca, from a trivial 3.9% to 43% after 1 month; however, during follow-up a progressive reduction, down to 14% occurs. As for PTH, cases at target increase from a basal zero value, to levels invariably <10% during the entire follow-up.

To take into account the possible individual fluctuations above, within or below the ranges, we also evaluated in each patient the probability of persisting at target. This was obtained by a survival curve based on the occurrence of at least two consecutive checks within the range. As shown in Figure 4, according to this method, the probability of persisting within the range was 21% after 1 month for Ca, with a tendency to reduction; 41% for P, with a tendency to average roughly 30% and practically zero for PTH.

Finally, considering the high prevalence of cases with low PTH values, we further examined the potential role respectively played on the occurrence of this specific target, by the type of surgery (i.e. total versus subtotal PTX) or by vitamin D therapy. As a whole, the mixed-effects model revealed that neither type of surgery nor vitamin D therapy was significantly associated with PTH levels. Moreover, as for surgery, no difference was evident in the probability of persisting within the ranges by examining separately patients submitted to either total or subtotal PTX. As for vitamin D, between 67 and 77% of the patients were prescribed calcitriol at any point during follow-up, at doses of 1.6 ± 1.0 μg/day after 1 month, tapering at 0.95 ± 0.7, 0.47 ± 0.3 and 0.49 ± 0.22 μg/day, respectively, 1, 3 and 5 years since surgery. These doses were identical to the ones prescribed to patients in the low PTH interval (1.6 ± 1.0 μg/day after 1 month and 0.9 ± 0.7; 0.4 ± 0.3 and 0.5 ± 0.2 μg/day, respectively, after 1, 3 and 5 years), who were not hypercalcaemic as indicated by their average values of serum Ca: 9.0 ± 0.9 mg/dl after 1 month and 9.3 ± 0.8; 9.3 ± 0.9 and 9.5 ± 0.9 mg/dl after 1, 3 and 5 years, respectively.

Discussion

A major challenge for the surgeons performing a parathyroidectomy to ureamic patients is to avoid persistence or recurrence of the disease. For this reason many of them choose total parathyroidectomy, with the awareness that true radical surgery is very difficult to accomplish (due to unnoticed extra-numeral glands or embryonic parathyroid residuals) [8]. In contrast, nephrologists favour subtotal parathyroidectomy (either as removal of three glands and five-sixths of the fourth or as removal of all identified glands followed by auto-transplantation), with the aim of avoiding permanent hypoparathyroidism [7,14]. As a matter of fact, recurrence or persistence rates are similar with either technique [9,15], while prevalence of hypoparathyroidism is not carefully considered. In this respect, we must underline that no specific range for PTH values after parathyroid surgery exists allowing us to define it as successful, and the authors empirically select different thresholds for classifying persistence, recurrence or even hypoparathyroidism [9,13,16]. Nowadays, since we are definitely worried about both very high or very low PTH values, the recommended PTH range after parathyroidectomy should be the same as the general ureamic population.

To our knowledge, data in the literature evaluating to what extent dialysis patients target the recommended NKF-K/DOQI^{TM} ranges for Ca, P and PTH after parathyroid surgery are limited to abstract reports and warn about the risk of reaching too low PTH values [17].

Our study indicates that the number of patients targeting the optimal 150–300 pg/ml PTH interval, up to 5 years since parathyroidectomy, is rather low. Significantly, the most frequently observed range is <150 pg/ml, indicating hypoparathyroidism as the prevailing clinical outcome. Notably, this result is not affected by the type of surgery, as if, on a practical ground, no dilemma should exist about surgical procedure. Alternatively, this undesirable outcome could be related to the ongoing vitamin D therapy, which, in our study, was always prescribed in at least two-thirds of the patients. However, no significant association resulted between the dose of calcitriol and PTH levels in the whole population as well as in the subgroup with low PTH values. Moreover, patients in the low PTH group were not hypercalcaemic. Therefore, although in some patients withdrawing of vitamin D could possibly be associated with an increase of PTH levels, this would also increase the risk of hypocalcaemia and then of recurrence of hyperparathyroidism.

The information that parathyroidectomy results mostly in hypoparathyroidism raises the question whether neck surgery should be definitely discouraged in uraemia. However, the potential risks of low PTH values and then of low turnover bone disease seem to be counter-balanced by the improved survival reported, in the long term, in dialysis patients submitted to parathyroidectomy [18,19]. This benefit can be explained by the number of positive clinical effects, e.g. on erythropoiesis [13,20], hypertension [13,21] and/or left-ventricular hypertrophy [22] described with this surgery, all referred to correction of severe hyperparathyroidism. Therefore, the physiopathology of clinical results after parathyroid surgery requires further investigations also aimed at defining if the recommended NKF-K/DOQI^{TM} ranges are optimal also in this subgroup of dialysis patients.

Our study also indicates that after parathyroidectomy serum levels of Ca mostly lay out of the recommended ranges while some improvement occurs for serum P. Compared to basal values, an evident drop is obtained for both parameters, as if the contributory role of high bone turnover had been weakened.

Finally, our data indicate that in the long term (>3–5 years) a tendency towards an increment of serum levels of PTH and Ca exists. This is in agreement with the not infrequently described phenomenon of disease recurrence after several years since surgery [8,9,16] and underlines the importance of medical surveillance and treatment even after surgical therapy. Conceivably, employment of calcimimetics or vitamin D analogs could definitely impact this outcome.

Being a single-centre study, a general conclusion on the adequate control of hyperparathyroidism after surgery is not allowed; nonetheless, the specificity of the topic is underlined, claiming for further, multi-centre studies.

We conclude that parathyroid surgery does not represent an optimal therapeutic tool for targeting the recommended NKF-K/DOQI^{TM} ranges for Ca, P and PTH. In particular, too low PTH values are frequently obtained, whose clinical effects deserve further studies. The possibility of a time-dependent risk for recurrence is confirmed.

Conflict of interest statement. None declared.

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