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Preoperative calcitriol reduces postoperative intravenous calcium requirements and length of stay in parathyroidectomy for renal-origin hyperparathyroidism ☆

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ABSTRACT

Background: Patients undergoing subtotal parathyroidectomy for renal-origin hyperparathyroidism often develop postoperative hypocalcemia, requiring calcitriol and intravenous calcium (Postop-IVCa). We hypothesized that in subtotal parathyroidectomy for renal-origin hyperparathyroidism, preoperative calcitriol treatment reduces the use of postoperative administration of intravenous calcium.

Methods: A retrospective chart review compared subtotal parathyroidectomy for renal-origin hyperparathyroidism patients who received preoperative calcitriol treatment with those patietns who did not receive preoperative calcitriol treatment at one institution. Preoperative calcitriol treatment loading doses were 0.5 mcg twice daily for 5 days. All patients received postoperative calcitriol and oral calcium carbonate. Postoperative administration of intravenous calcium was given for symptoms, calcium <7.0 mg/dL, or surgeon preference. The Fisher exact test was used to compare proportions. The Wilcoxon test was used to compare continuous data. Multivariable logistic regression adjusted for confounders.

Results: Included were 81 patients who received subtotal parathyroidectomy for renal-origin hyperparathyroidism (41 patients who received preoperative calcitriol treatment, 40 patients who did not receive preoperative calcitriol treatment). Preoperative calcitriol treatment use increased over time (0% 2004–2010, 69% 2011–2016). Groups who received preoperative calcitriol treatment and groups who did not receive preoperative calcitriol treatment were similar in preoperative serum calcium, vitamin D, parathyroid hormone, and median age ($P > .05$ for all). Patients who received preoperative calcitriol treatment less often required postoperative administration of intravenous calcium (34% vs 90% of patients who did not receive preoperative calcitriol treatment, $P < .001$). Median length of stay was 2.0 days shorter for patients who received preoperative calcitriol treatment versus patients who did not receive preoperative calcitriol treatment patients ($P < .001$). Factors associated with postoperative administration of intravenous calcium included not receiving preoperative calcitriol treatment, low preoperative calcium, and high preoperative parathyroid hormone. After multivariable adjustment, preoperative calcitriol treatment remained independently associated with reduced postoperative administration of intravenous calcium (OR 0.02, $P < .001$).

Conclusion: Preoperative calcitriol therapy lowered use of postoperative administration of intravenous calcium by 56% and length of stay by 50% in subtotal parathyroidectomy for renal-origin hyperparathyroidism patients. We believe preoperative calcitriol treatment should become standard of care for subtotal parathyroidectomy for renal-origin hyperparathyroidism.

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Introduction

First described in 1935, renal-origin hyperparathyroidism results from a constellation of biochemical abnormalities in chronic kidney disease.[1] Advances in medical management for this

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condition and improved dialysis access and delivery reduced the need for parathyroidectomy in patients with renal-origin hyperparathyroidism (PTXRO).[2–4] Nevertheless, PTXRO remains necessary when symptoms of hypercalcemia are refractory to medical therapy, drug costs are prohibitive, when patients cannot adhere to medical treatment, or when optimization before renal transplantation is time sensitive.[5–7]

Postoperative hypocalcemia is the most common morbidity after PTXRO.[8,9] Broadly referred to as "hungry bone syndrome," its pathophysiology relates to a sudden decline in circulating parathyroid hormone (PTH) levels after surgery, causing a surge in calcium uptake because of bone remineralization.[5,8,10,11] This process can create profound hypocalcemia with clinical manifestations of neuromuscular irritability, muscle cramping, mental status changes, and cardiac arrhythmias, which mandate aggressive replacement of depleted skeletal calcium stores.[12] Commonly, this is achieved through postoperative administration of intravenous calcium (postop-IVCa) and supplementation with active vitamin D metabolites, such as calcitriol (1,25-dihydroxycholecalciferol).[13,14] Postoperative hypocalcemia impacts hospital length of stay (LOS), because patients require ongoing hospitalization for intravenous therapies and monitoring. Even with pre-emptive standardized postop-IVCa treatment, LOS and use of postop-IVCa remain high.[15]

Several small studies proposed preoperative vitamin D loading to mitigate severe postoperative hypocalcemia, but this practice has not gained wide acceptance because the studies yielded conflicting results.[16–18] Immediate postoperative calcitriol loading has been proposed to reduce postoperative hypocalcemia.[18] A limitation of postoperative calcitriol treatment, however, is that its onset of activity may take up to 48 hours.[12] As calcitriol is effective in the postoperative setting, to avoid this delay in onset and attempt to alleviate postoperative hypocalcemia, our group began prescribing preoperative calcitriol loading doses in 2011. In this study we sought to test the hypothesis that in PTXRO, preoperative calcitriol treatment reduces postop-IVCa use.

Methods

Medical records of all patients at a single institution, undergoing PTXRO between September 2004 and December 2016 were retrospectively reviewed. Demographics, preoperative and postoperative laboratory values, postoperative intravenous calcium requirements, length of hospital stay, complications, and 30-day readmissions were abstracted. Complications included any adverse event within 30 days of surgery (except hypocalcemia, which is described separately) or reoperation. Readmissions were those noted at the study institution from review of records, or at other institutions as reported by patients. Indications for parathyroidectomy included renal-origin hyperparathyroidism refractory to medical treatment, calciphylaxis, or optimization for kidney transplant.

Preoperative calcitriol treatment

During the study period, some patients received preoperative calcitriol (PC) loading doses, and others did not. When given, PC loading was administered at 0.5 mcg twice daily for 5 days before surgery.

Surgical procedure

Dialysis patients were dialyzed the day before their operation. All patients received preoperative parathyroid gland imaging. Patients underwent bilateral neck exploration to identify all glands, and subtotal parathyroidectomy was performed. The gland appearing least hyperplastic, but with adequate blood supply, was partially resected and marked with a titanium clip. For removed parathyroid glands, parathyroid tissue was verified by rapid parathyroid hormone assay or frozen section. Intraoperative serum intact parathyroid hormone level monitoring confirmed a drop of PTH to below 300 pg/mL, or by at least 90%, as recommended by Kidney Disease: Improving Global Outcomes guidelines.[19]

Perioperative treatment strategy

Regardless of preoperative treatment, all patients received postoperative oral calcium carbonate (elemental calcium carbonate 2.5g four times per day) and oral vitamin D (calcitriol starting from 0.5 mcg twice daily). Calcitriol doses were titrated based on serum calcium levels up to 4 mcg per day. Serum calcium levels were monitored in the recovery room, at 10 pm on the day of surgery, then every 12 hours or daily to adjust calcitriol and calcium treatment. Intravenous calcium supplementation was initiated for serum calcium below 7.0 mg/dL, symptomatic hypocalcemia, or surgeon preference. The 7.0 mg/dL threshold was adopted based on the experience of the senior surgeon (E.L.K.). Intravenous calcium consisted of 100 mL 10% calcium gluconate (900 mg elemental calcium) in 500 mL of 5% dextrose water, infused at a rate of 30 mL/hour, which was tapered as serum calcium and symptoms stabilized. Length of stay was from the day of surgery until hospital discharge. Patients were discharged when calcium levels normalized, and no hypocalcemia symptoms existed.

Statistical analysis

Outcomes of patients who did and did not receive PC were compared. The Fisher exact test was used to compare proportions, and the Wilcoxon rank sum or Welch t tests were used to compare continuous variables, as appropriate. Univariate logistic regression determined the association of individual clinical features with receipt of postoperative IV calcium. Factors showing association at $P < .1$ were considered for inclusion in a multivariable logistic regression model. The Benjamini-Hochberg false-discovery rate correction was used to adjust P values for multiple comparisons, as appropriate.[20] The University of Chicago Institutional Review Board (Chicago, IL) approved this study (IRB-16-0379).

Results

Included were 81 patients who underwent subtotal parathyroidectomy for renal-origin hyperparathyroidism. Of these, 77 had secondary hyperparathyroidism attributable to end-stage renal disease and dialysis (95%), and 4 had tertiary hyperparathyroidism after renal transplantation (Fig. 1). During the study period, use of PC loading for patients undergoing parathyroidectomy for ROHPT was adopted on a per-surgeon basis and increased over time. No specific criteria selected patients for PC. In the early portion of the study, no patients received PC (0% PC use in 2004–2010). In 2011, PC was initiated and from 2011 to 2016, 69% of patients received PC. By the end of the study period, most patients received PC (76.2% in 2015–2016), but not all. The most common reason for not receiving PC in this later period was denial of coverage for PC by insurance. Of the 81 total patients, 41 (51.2%) received preoperative calcitriol (PC group) and 40 did not (no preoperative calcitriol, NPC group).

Preoperative patient characteristics were similar between the PC and NPC groups (Table 1). Median age was 47.0 years in the NPC group and 45.0 years in the PC group ($P = 1$). Female patients comprised 62.5% of the NPC group and 61.0% of the PC group ($P = 1$). Median preoperative calcium and PTH levels were 9.3 mg/dL and 1,914 pg/mL in the NPC group vs 9.4 mg/dL and 1,655 pg/mL in the PC group ($P = .8$ for both). There was a trend toward lower

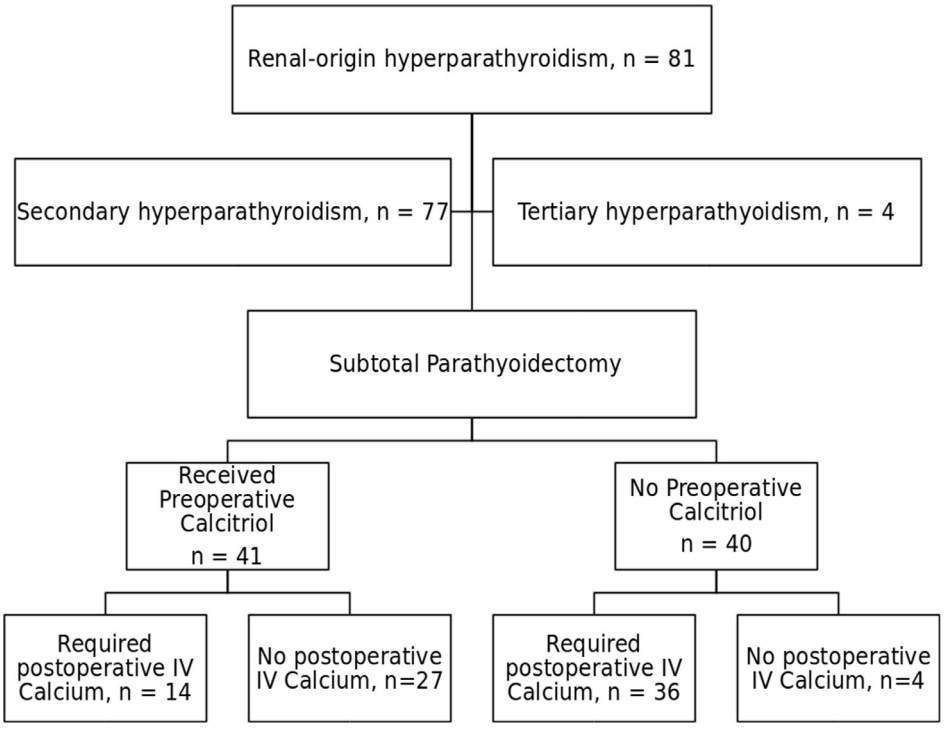

Fig. 1. Study profile.

Table 1
Baseline demographics and clinical data*.

Variable	NPC ($n=40$)	PC ($n=41$)	Unadjusted P value	FDR-adjusted P value
Age, median years (IQR)	47.0 (35.5–55.0)	45.0 (37.0–47.2)	.8	1
Sex (female)	25 (62.50%)	25 (61%)	1	1
Preoperative calcium, median mg/dL (IQR)	9.25 (8.575–9.8)	9.4 (8.8–9.8)	.5	.8
Preoperative PTH, median pg/mL (IQR)	1,914 (1,193–2,447)	1,655 (1,302–2,092)	.5	.8
Preoperative vitamin D, median ng/mL (IQR)	16.0 (11.0–23.0)	21.0 (14.2–35.5)	.051	.2

* P values reflect comparison between PC and NPC groups and are presented with FDR adjustment.
FDR, false-discovery-rate; *IQR*, interquartile range.

preoperative vitamin D levels in the NPC group. This difference approached but did not reach significance in the unadjusted analysis (21.0 vs 16.0 ng/mL, $P=.051$ unadjusted, $P=.2$ after adjustment for multiple comparisons).

Surgical outcomes

Subtotal parathyroidectomy was performed in all patients. One patient underwent an additional planned robotic mediastinal exploration for an intrathoracic gland that was identified on preoperative imaging. Complication rates were similar between NPC and PC groups (three patients in each). In the NPC group, complications included a deep venous thrombosis, a thrombosed dialysis fistula, and an unplanned reintubation. In the PC group there was a reoperation for neck hematoma, requiring evacuation in a patient anticoagulated for pulmonary embolism, one unilateral vocal fold paresis requiring injection, and one patient whose PTH failed to drop below 300pg/mL.

Initial postoperative serum calcium levels trended lower in the NPC group, (median 7.4 vs 7.7 mg/dL, $P=.2$). Final intraoperative PTH levels were higher in the PC group (median 136.0 vs 88.5 pg/mL, unadjusted $P=.06$), and postoperative PTH levels on the evening of surgery were higher in the NPC group (median 58.5 vs 53.0 pg/mL, unadjusted $P=.7$). Neither difference was statistically significant (Table 2).

Although only small differences existed in postoperative laboratory values between NPC and PC groups, rates of symptomatic hypocalcemia requiring IV calcium showed a significant difference. Whereas 36 of 40 patients who did not receive preoperative calcitriol (90%) required IV calcium, only 14 of 41 patients who did receive PC required postoperative IV calcium treatment (34.1%, $P < .001$). Although the longest duration of IV calcium use was 11 days in a patient in the PC group, most PC group patients required no IV calcium (Fig. 2), and the median duration of IV calcium treatment was shorter for those receiving preoperative calcitriol (median 3 days for NPC patients, 0 days for PC patients, $P < .001$) (Table 2).

Total hospital LOS was significantly shorter in the PC group. Again, a PC patient had the longest overall LOS (21 days), but most PC patients stayed in the hospital for only 1 or 2 days. No NPC patients were discharged on postoperative day 1 (Fig. 3). When comparing the NPC group with the PC group, median LOS was 2 full hospital days shorter for patients who received PC (median 4.0 days in NPC group vs 2.0 days in PC group, $P = .001$). Administration of postop-IVCa seemed to drive this difference. When analyzed without consideration of calcitriol treatment, patients who required postop-IVCa had a median LOS of 4.0 days vs 2.0 days in those who did not. The same was true when NPC patients were examined alone. Median LOS was 2.0 days for NPC patients who did not require postop-IVCa vs 4.0 days among those who did. To determine whether differences in discharge practices over time

Table 2
Laboratory values, IV calcium requirements, length of stay, nonhypocalcemia complications, and readmissions in NPC and PC groups*.

Variable	NPC ($n = 40$)	PC ($n = 41$)	Unadjusted *P* value	FDR-adjusted *P* value
Lowest Intraoperative PTH, median pg/dL (IQR)	88.5 (61.5–147.2)	136.0 (86.0–222.0)	.06	.2
Postoperative Calcium, median mg/dL (IQR)	7.4 (6.6–7.9)	7.7 (6.9–8.5)	.09	.2
Postoperative PTH, median pg/mL (IQR)	58.5 (26.5–130.0)	53.0 (27.0–104.0)	.7	1
Required Postop-IVCa	36/40 (90%)	14/41 (34.1%)	**< .001**	**< .001**
Duration of Postop-IVCa, median days (IQR)	3.0 (1–3.3)	0.0 (0.0–1.0)	**< .001**	**< .001**
Length of Hospital Stay, median days (IQR)	4.0 (3.0–6.0)	2.0 (1.0–3.0)	**< .001**	**.001**
Complications within 30 days (yes/total)	3/40	3/41	1	1
Readmission within 30 days (yes/total)	(10/40) 25.0%	(7/41) 17.1%	.4	.8

* *P* values are shown with FDR adjustment.
FDR, false-discovery-rate; *IQR*, interquartile range.

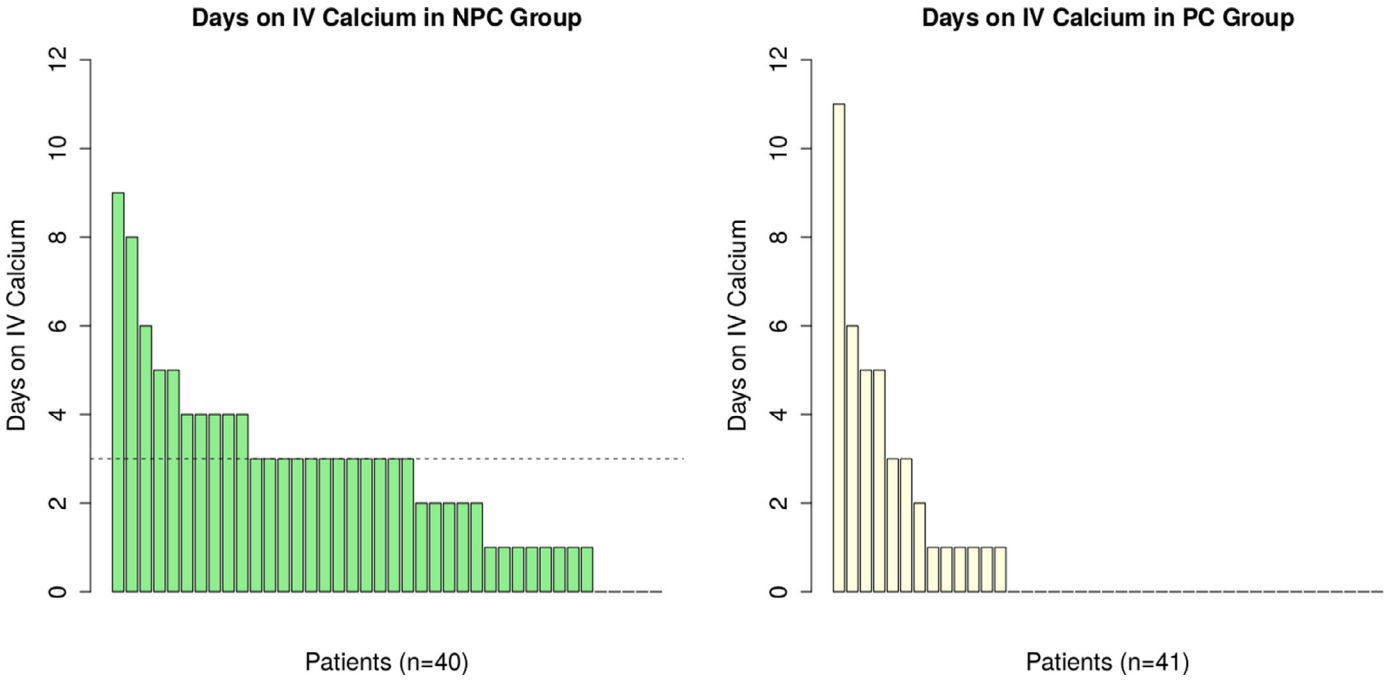

Fig. 2. Duration of IV calcium administration in patients who did not receive preoperative calcitriol (NPC group; *left panel*) and those who received preoperative calcitriol (PC group; *right panel*). Median days of IV calcium are indicated by the *dashed horizontal line*. For the PC group, the median was 0 days.

affected LOS, LOS in patients treated after 2010 was examined. This revealed that median LOS overall was 3.0 days. In patients who did not require postop-IVCa, median LOS remained 2.0 days, but rose to 5.0 days for those who did require it. Readmission rates were similar between the NPC and PC groups (25.0 vs 17.1%, $P = .8$). In the NPC group, all 10 readmissions were for treatment of hypocalcemia, and in the PC group, 3 of 7 were for other diagnoses (upper gastrointestinal bleeding, hyperkalemia, and shortness of breath).

Regression models

To determine clinical characteristics associated with postop-IVCa, univariate logistic regression was performed. By this analysis, factors associated with postop-IVCa treatment included lower preoperative serum calcium, higher preoperative PTH ($P = .009$ for both), and not receiving preoperative calcitriol ($P < .001$; Table 3). Of note, because different surgeons could vary in technical aspects of the operation or in their threshold for administering IV calcium, the association among individual surgeons and receipt of IV calcium was examined with no significant correlation identified. Intraoperative and postoperative PTH levels did not correlate with postop-IVCa. Preoperative vitamin D levels, which showed a trend toward lower levels in the NPC group, similarly showed no correlation with the need for postop-IVCa on univariate analysis.

To assess whether imbalances in other factors correlating with receipt of postoperative IV calcium might explain the large difference in rates of IV calcium treatment between the NPC and PC groups, multivariable logistic regression was performed. The model included factors showing significant correlation on univariate analysis with postoperative IV calcium use. After controlling for preoperative serum calcium and PTH levels, preoperative calcitriol treatment remained strongly associated with decreased

Table 3
Univariate analysis of characteristics associated with need for Postop-IVCa.

Variable	OR (95% CI)	*P value*
Age	0.98 (0.94–1.01)	.1
Sex	0.97 (0.39–2.47)	.9
Preoperative calcium	0.42 (0.21–0.77)	**.009**
Preoperative PTH*	2.92 (1.45–6.55)	**.009**
Preoperative calcitriol (PC)	0.06 (0.01–0.18)	**< .001**
Preoperative vitamin D	1.00 (0.96–1.03)	.8
Surgeon (Surgeon A reference)	1.00 (NA)	.4
Surgeon B	1.82 (0.66–2.25)	—
Surgeon C	1.89 (0.66–5.80)	—
Final intraoperative PTH	1.00 (0.995–1.00)	.4
Postoperative PTH	1.00 (0.995–1.00)	.4

* Preoperative PTH is transformed on a base-2 log scale. The OR therefore reflects risk of receiving postoperative IV calcium for each doubling of preoperative PTH.
OR, odds ratio; *CI*, confidence interval; *NA*, not applicable.

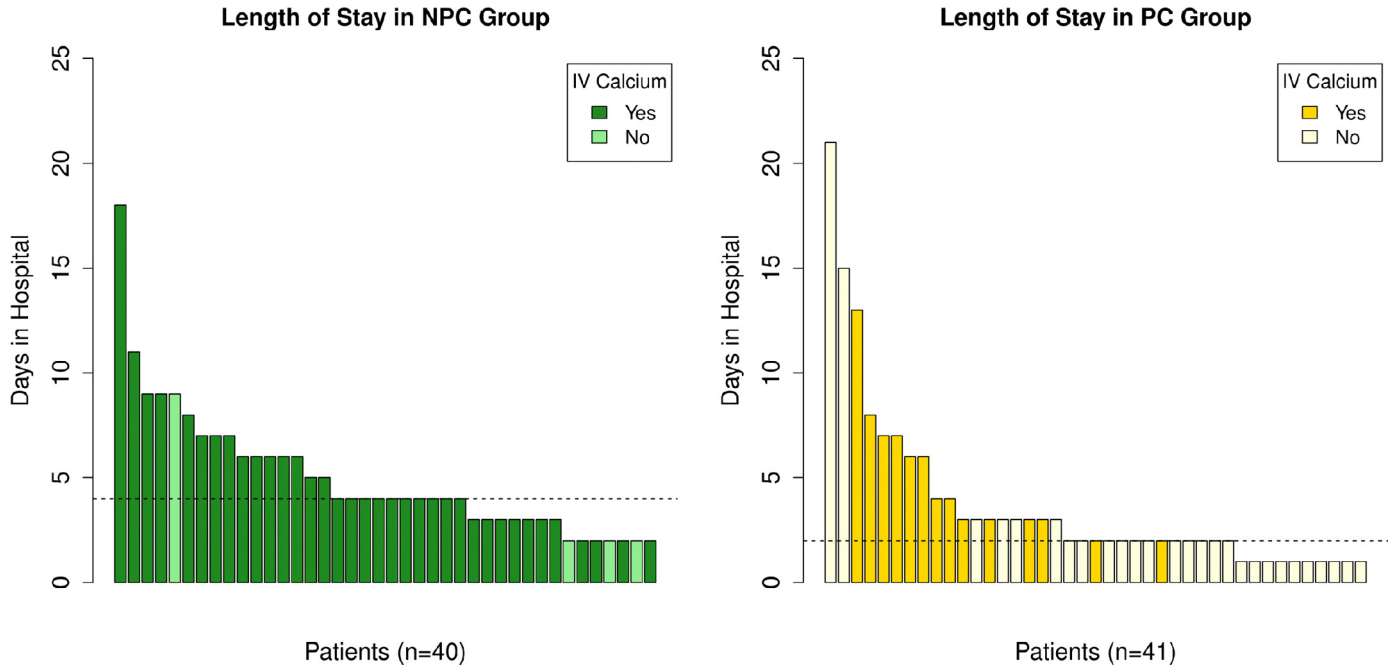

Fig. 3. Hospital length of stay in patients who did not receive preoperative calcitriol (NPC group; *left panel*) and those who received preoperative calcitriol (PC group; *right panel*). Median length of stay is indicated by the *dashed horizontal line*. Within each group, the different colors shown in the *legend* indicate which patients required postoperative intravenous calcium (IV Calcium). Median length-of-stay was shorter in PC patients, and most PC patients with longer length-of-stay were those who required IV Calcium.

Table 4
Multivariable logistic regression analysis of factors associated with increased postop-IVCa requirement.

Variable	OR (95% CI)	*P value*
Preoperative calcitriol (PC)	0.020 (0.0023–0.097)	**< .001**
Preoperative calcium	0.22 (0.065–0.57)	**.005**
Preoperative PTH*	7.34 (2.34–31.2)	**.002**

* Preoperative PTH is transformed on a base-2 log scale. The OR therefore reflects risk of receiving postoperative IV calcium for each doubling of preoperative PTH.

OR, odds ratio; *CI*, confidence interval.

postoperative IV calcium use, with an odds ratio of 0.020 (95% confidence interval 0.0023–0.097, $P < .001$; Table 4). Preoperative serum calcium and PTH levels were also independently associated with the risk of receiving postop-IVCa. Higher preoperative calcium levels gave a lower risk of requiring postop-IVCa, and higher preoperative PTH levels increased the risk of needing postop-IVCa.

Discussion

In patients undergoing PTXRO, the present study found that a short course of PC loading correlated with a dramatically lower need for postop-IVCa compared with patients who did not receive PC. With fewer days on IV calcium treatment, median hospital LOS for PC patients fell to 2.0 days compared with 4.0 days for NPC patients.

Postoperative hypocalcemia is the most common morbidity leading to increased LOS after PTXRO. Although postoperative oral calcium and calcitriol may be sufficient in some PTXRO patients to avoid hypocalcemia, many require intravenous calcium. For patients with primary hyperparathyroidism, severe postoperative hypocalcemia remains much less common; however, PTXRO patients experience rates of postoperative hypocalcemia in excess of 80%, with associated median LOS reported between 4.7 and 10.2 days after surgery.[8,16,21,22] The potentially severe complications of untreated hypocalcemia warrant aggressive therapy, and often days of postop-IVCa treatment are necessary.[16] This in turn results in longer stays and greater healthcare costs. Hence, understanding and mitigating postoperative hypocalcemia promises to improve both patient symptoms and the economic burden of secondary and tertiary hyperparathyroidism.

To reduce clinical hypocalcemia in the immediate postoperative period, several studies have shown a benefit to postoperative calcitriol treatment in PTXRO.[16,18,23] Calcitriol is the hormonally active metabolite of vitamin D. It regulates expression of TRPV6, which is a calcium entry channel responsible for calcium absorption in the intestine.[24] By increasing intestinal absorption, calcitriol helps to raise serum calcium.[12] In a small prospective randomized study, both the drop in serum calcium concentration and the calcium replacement dose were significantly less in patients treated with oral calcitriol immediately after parathyroidectomy.[23] Although not statistically significant, the findings by Ho et al.[8] also demonstrated that patients receiving preoperative active vitamin D analogues required less postoperative calcium. Niramitmahapanya et al.[18] found that, although 90% of PTXRO patients required postop-IVCa, those who received loading doses of calcitriol immediately after surgery required less total IV calcium.[18]

Despite the efficacy of PC in treating postoperative hypocalcemia, a major drawback to the current standard of PC treatment concerns its onset time of 1 to 2 days.[12] Even with large postoperative loading doses, if calcitriol does not raise calcium levels for 2 days, a window exists for severe hypocalcemia to develop. A benefit for preoperative administration of calcitriol has not been well documented in the literature; however, given calcitriol's effectiveness in the postoperative period, our group reasoned that beginning loading doses of calcitriol several days before PTXRO might help patients avoid this onset lag. We therefore adopted a short course of preoperative calcitriol for patients with planned PTXRO, in addition to the standard postoperative dose.

Rates of postop-IVCa use of 90% and median LOS of 4.0 days in the NPC group in this study closely match published reports. The

rate of postop-IVCa use fell to 36% in patients treated with PC, with a concomitant reduction in hospital LOS to 2.0 days. Differences in LOS seemed to be related to lower rates of postop-IVCa use in the PC group. Even in NPC patients, LOS was 2.0 days among those not requiring postop-IVCa. An alternative explanation for shorter LOS in the PC group would be that unrelated trends toward shorter hospitalizations drove faster discharges in PC patients who tended to be treated more recently. Arguing against this was the finding that, when only patients treated after 2010 were considered, the same difference in LOS existed based on postop-IVCa receipt (median 2.0 days in no postopIVCa patients vs 5.0 with treatment). Finally, if patients were inappropriately hurried out of the hospital, more readmissions would be expected. Although it is possible that readmissions to other facilities unreported by patients existed, that the PC group actually had lower readmission rates than the NPC group, and fewer readmissions for hypocalcemia, argues that faster discharges were indeed attributable to better control of hypocalcemia with PC.

Although we believe that PC administration caused these effects, a major limitation of this study is its nonrandomized and retrospective design, meaning that imbalances between treatment group characteristics or unmeasured selection factors could also influence outcomes. To address this limitation, factors also potentially contributing to postoperative hypocalcemia, such as preoperative serum calcium, PTH, and vitamin D levels were examined. Of these, both preoperative PTH and calcium levels strongly correlated with receipt of postop-IVCa, but median levels of these showed no difference between the PC and NPC groups. Preoperative vitamin D levels did show some imbalance between the PC and NPC groups, but preoperative vitamin D levels did not correlate with postop-IVCa when tested in the univariate analysis. To further address these concerns, the multivariable model adjusted for preoperative calcium and PTH levels, and after accounting for these confounders, which were associated with postop-IVCa, the effect of PC treatment appeared stronger than it did by univariate analysis (multivariable OR 0.02 vs 0.06 on univariate analysis). Finally, as surgeons' individual practices might vary, we tested the effect of the different surgeons in the study on postop-IVCa, and this likewise did not correlate with the outcome. Thus, potential confounders were controlled for as far as possible, suggesting that reductions in postop-IVCa were attributable to PC treatment.

The most definitive evidence that PC reduces postop-IVCa requirements would come from a randomized, controlled trial. Using the effect size demonstrated in this study, a preliminary power calculation indicates that as few as 30 patients could be randomized to demonstrate efficacy, with 80% power and an alpha of 0.05. With more conservative assumptions of 80% of NPC patients and 50% of PC patients requiring postop-IVCa, the number of required patients jumps to 90. Patient accrual for such a trial could be difficult given the relative rarity of PTXRO and minimal drawbacks to simply prescribing PC, but with multi-institutional cooperation, it could be feasible.

In conclusion, hypocalcemia secondary to chronically depleted bone remains the most common complication after parathyroidectomy for patients with renal-origin hyperparathyroidism. The present study demonstrates that a short preoperative course of calcitriol loading for patients undergoing PTXRO reduces the absolute risk of need for postoperative intravenous calcium by 56% and hospital LOS by 50%. These results provide a justification for further randomized studies to corroborate these effects; however, given the ease and availability of providing PC, PC should be considered to become standard of care in PTXRO.

References

1. Pappenheimer AM, Wilens SL. Enlargement of the parathyroid glands in renal disease. *Am J Pathol*. 1935;11:73–91.
2. Arevalo-Lorido JC, Carretero-Gomez J, Garcia-Sanchez F, Macia-Botejara E, Ramiro-Lozano JM, Masero-Carretero A, et al. Secondary hyperparathyroidism prevalence and profile, between diabetic and non-diabetic patients with stage 3 to 4 chronic kidney disease attended in internal medicine wards. *MiPTH study. Diabetes Metab Syndr*. 2016;10(2 Suppl 1):S16–S21.
3. Komaba H, Kakuta T, Fukagawa M. Management of secondary hyperparathyroidism: How and why? *Clin Exp Nephrol*. 2017;21(Suppl 1):37–45.
4. Komaba H, Taniguchi M, Wada A, Iseki K, Tsubakihara Y, Fukagawa M. Parathyroidectomy and survival among Japanese hemodialysis patients with secondary hyperparathyroidism. *Kidney Int*. 2015;88:350–359.
5. Albuquerque RFC, Carbonara CEM, Martin RCT, Dos Reis LM, do Nascimento CPJ, Arap SS, et al. Parathyroidectomy in patients with chronic kidney disease: Impacts of different techniques on the biochemical and clinical evolution of secondary hyperparathyroidism. *Surgery*. 2018;163:381–387.
6. Foley RN, Li S, Liu J, Gilbertson DT, Chen SC, Collins AJ. The fall and rise of parathyroidectomy in U.S. hemodialysis patients, 1992 to 2002. *J Am Soc Nephrol*. 2005;16:210–218.
7. Savazzi GM, Allegri L. The hungry bone syndrome: Clinical problems and therapeutic approaches following parathyroidectomy. *Eur J Med*. 1993;2:363–368.
8. Ho LY, Wong PN, Sin HK, Wong YY, Lo KC, Chan SF, et al. Risk factors and clinical course of hungry bone syndrome after total parathyroidectomy in dialysis patients with secondary hyperparathyroidism. *BMC Nephrol*. 2017;18:12.
9. Torer N, Torun D, Torer N, Micozkadioglu H, Noyan T, Ozdemir FN, et al. Predictors of early postoperative hypocalcemia in hemodialysis patients with secondary hyperparathyroidism. *Transplant Proc*. 2009;41:3642–3646.
10. Westerdahl J, Lindblom P, Valdemarsson S, Tibblin S, Bergenfelz A. Risk factors for postoperative hypocalcemia after surgery for primary hyperparathyroidism. *Arch Surg*. 2000;135:142–147.
11. Witteveen JE, van Thiel S, Romijn JA, Hamdy NA. Hungry bone syndrome: Still a challenge in the post-operative management of primary hyperparathyroidism: A systematic review of the literature. *Eur J Endocrinol*. 2013;168:R45–R53.
12. Shoback D. Clinical practice. Hypoparathyroidism. *N Engl J Med*. 2008;359:391–403.
13. Rathi MS, Ajjan R, Orme SM. A case of parathyroid carcinoma with severe hungry bone syndrome and review of literature. *Exp Clin Endocrinol Diabetes*. 2008;116:487–490.
14. Viaene L, Evenepoel P, Bammens B, Claes K, Kuypers D, Vanrenterghem Y. Calcium requirements after parathyroidectomy in patients with refractory secondary hyperparathyroidism. *Nephron Clin Pract*. 2008;110:c80–c85.
15. Cheng SP, Liu CL, Chen HH, Lee JJ, Liu TP, Yang TL. Prolonged hospital stay after parathyroidectomy for secondary hyperparathyroidism. *World J Surg*. 2009;33:72–79.
16. Cozzolino M, Gallieni M, Corsi C, Bastagli A, Brancaccio D. Management of calcium refilling post-parathyroidectomy in end-stage renal disease. *J Nephrol*. 2004;17:3–8.
17. Heath DA, Van't Hoff W, Barnes AD, Gray JG. Value of 1-alpha-hydroxy vitamin D3 in treatment of primary hyperparathyroidism before parathyroidectomy. *Br Med J*. 1979;1:450–452.
18. Niramitmahapanya S, Sunthornthepvarakul T, Deerochanawong C, Sarinnapakorn V, Athipan P. Role of loading calcitriol to control hypocalcemia after parathyroidectomy in chronic kidney disease. *J Med Assoc Thai*. 2011;94:295–302.
19. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(4 Suppl 3):S1–201.
20. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. *Stat Med*. 1990;9:811–818.
21. Lorenz K, Ukkat J, Sekulla C, Gimm O, Brauckhoff M, Dralle H. Total parathyroidectomy without autotransplantation for renal hyperparathyroidism: Experience with a qPTH-controlled protocol. *World J Surg*. 2006;30:743–751.
22. Mittendorf EA, Merlino JI, McHenry CR. Post-parathyroidectomy hypocalcemia: Incidence, risk factors, and management. *Am Surg*. 2004;70:114–119.
23. Clair F, Leenhardt L, Bourdeau A, Zingraff J, Robert D, Dubost C, et al. Effect of calcitriol in the control of plasma calcium after parathyroidectomy. A placebo-controlled, double-blind study in chronic hemodialysis patients. *Nephron*. 1987;46:18–22.
24. Balesaria S, Sangha S, Walters JR. Human duodenum responses to vitamin D metabolites of TRPV6 and other genes involved in calcium absorption. *Am J Physiol Gastrointest Liver Physiol*. 2009;297:G1193–G1197.

Discussion

Dr Sally E. Carty (Pittsburgh, PA): Excellent paper. We do the same thing. Lots of dialysis patients actually get their meds through the dialysis center, which often takes up to 3 weeks. So you have to factor that in when starting them on preop calcitriol because otherwise they will just show up for surgery having never started.

You are treating vitamin D deficiency. Why don't you measure vitamin D?

Dr Salman K. Alsafran: We actually measured the vitamin D levels, and there was no significant difference between the 2 groups.

When we looked at the 2 groups, the patients who did not receive the calcitriol had a lower average vitamin D level of 16 versus 20. But this was not statistically significant.

Dr Scott Wilhelm (Cleveland, OH): Very nice paper. We have started doing this too after I talked to Dr. Carty.

Did you also look at alkaline phosphatase levels in your patients? One of the things that we have seen is that our patients with the really bad bone hunger syndrome that wind up in the hospital for a week on calcium, are often the same people with an alkaline phosphatase above 400 or 500.

Also, your data might be even more significant than what you showed, because 2 of your patients were high outliers for length of stay. Can you just give us a little bit of information like what increased their length of stay? I applaud you for keeping them in, because you should. But did you also take them out and see what happened to your mean length of stay without those two patients?

Dr Salman K. Alsafran: We did not analyze the alkaline phosphatase level in our cohort, but we probably should. When we do a randomized study, we probably should include it in the variables.

For the second question about the two patients in the preoperative calcitriol group, one of them actually had a pulmonary embolism and required longer hospitalization. She ended up having a neck hematoma, and had to be taken back to the OR to evacuate it. We actually did remove them from the analysis, and the median did not change.

Dr John Lew (Miami, FL): Congratulations to you and your colleagues for a nice study and presentation.

A lot of times when we treat these patients and anticipate significant postoperative hypocalcemia or hungry bone syndrome, we also manage these patients with high calcium baths during postoperative dialysis. Did you take that into consideration in your study? And did the calcitriol also reduce the need for high calcium bath postoperatively along with the intravenous calcium?

Dr Salman K. Alsafran: If the patients ended up needing dialysis in the hospital, all of the patients with low calcium had a high calcium dialysis bath. As you know, this strategy is temporary just like the IV calcium.

This did not matter because both groups who stayed longer in the hospital received the high calcium bath. We should actually look into this for the groups who left before dialysis, as maybe they did not receive the high calcium bath dialysis.

Dr Michael Campbell (Sacramento, CA): Great presentation. I just have two quick questions about your study design to make sure I understand it correctly:

Were any of these patients transplanted before getting their renal hyperparathyroidism operations? I find those patients are managed much differently postoperatively.

Also, you used a threshold of 7 mg/dL to start your IV calcium, which is a little higher than I typically use. Did your routine also prevent the patients from drifting down to those critical levels of calcium in the 6s or 5s, which we sometimes see with these patients?

Dr Salman K. Alsafran: Was anybody transplanted? Yes, we had four patients who had a transplantation.

Dr Michael Campbell (Miami, FL): Do you mean they had a kidney transplant before having the parathyroid operation?

Dr Salman K. Alsafran: And three of those patients were in the preoperative calcitriol group.

Dr Michael Campbell (Miami, FL): Did you also find that your protocol kept patients from dropping into the critically low calcium range such as the 5s and 6s? In other words, did you notice fewer critical postoperative hypocalcemia values in the calcitriol group?

Dr Salman K. Alsafran: Absolutely. We had one or two who actually dropped into the low 5s, but the majority of them, even if they dropped, were in the 6s. But in the other group, some of them even had critical levels in the 4s. Some of them did not drop a lot, but the majority of them were in the 5s and 6s.

Dr Willemijn Van Der Plas (Groningen, Netherlands): I have a question about the indications or criteria to start IV calcium since you said that it was also due to the surgeon's preference.

Could you elaborate on how many of the patients were started on IV calcium due to the surgeon's preference and not due to documented low calcium levels?

And to follow up with that, could it be possible that surgeons who started calcitriol before the surgery actually thought they may have already prevented hypocalcemia, so they were more reluctant to start IV calcium? That could have caused a difference between the two groups.

Dr Salman K. Alsafran: Yes. We looked the trend of total calcium level, and, if there was a major drop, say it was about 8.1 and the next level 6 or 12 hours later dropped to 7.1 or 6.9, then the surgeon would consider it a major drop, and they would start IV calcium, as the level was just going to go lower.

The other question was about surgeons who did not administer calcitriol. There is no way we could have looked into this because the study is retrospective. But when we design our clinical trial, we probably will include this.

Dr Adam Kabaker (Chicago, IL): This is also how we practice.

My question for you is whether you separated out the peritoneal dialysis patients from the hemodialysis patients. At least at our institution, I find they behave very differently.

The peritoneal dialysis patients are very much more hypocalcemic, more difficult to control because you can't do the high calcium bath. Also, I think that 90% of patients receiving IV calcium seems a little high, at least at our institution.

Do you follow ionized calcium levels for these patients? Or are these corrected calciums?

Dr Salman K. Alsafran: All of our patients were on hemodialysis. None of our patients were on peritoneal dialysis.

For the second question, we were following total calcium. We did not follow the ionized calcium.