Management of calcium refilling post-parathyroidectomy in end-stage renal disease

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ABSTRACT: Background: Management of post-parathyroidectomy hypocalcemia in dialysis patients is not well defined. We reviewed published approaches to treatment in an effort to define a clinical algorithm for controlling serum calcium levels post-operatively.

Methods: We conducted a PubMed search for the years 1980-2003 with the keywords “hypocalcemia” and “parathyroidectomy”. Only English language and human subject abstracts were analyzed, and only those articles dealing with secondary or tertiary hyperparathyroidism (HPTH) were reviewed further. Other articles were extracted from cross-referencing.

Results: We initially examined 146 articles. This review summarizes the findings of the relevant articles along with our own practice regarding post-parathyroidectomy hypocalcemia management in dialysis patients. The vast majority of patients require intravenous (i.v.) calcium supplements after surgery. There are no available controlled studies on calcium supplementation for post-parathyroidectomy hypocalcemia in this patient population. Calcitriol supplementation proved valuable in two studies.

Conclusions: Post-parathyroidectomy hypocalcemia is a common complication, which can be prevented and treated with oral and i.v. calcium supplementation and/or active vitamin D metabolites. Daily follow-up of both serum calcium and phosphorus are mandatory to prevent this major post-operative complication. Based on the available evidence, we propose a protocol for the prevention and treatment of post-parathyroidectomy hypocalcemia, for use in clinical practice. This approach requires validation by a controlled clinical trial.

Key words: Hypocalcemia, Hyperparathyroidism, Dialysis, Calcitriol

INTRODUCTION

In end-stage renal disease (ESRD) patients, parathyroid hyperplasia and high circulating parathyroid hormone (PTH) levels characterize secondary hyperparathyroidism (HPTH) (1-5). Several vitamin D metabolites have been used in the treatment of secondary HPTH because of their efficacy in suppressing both PTH secretion and synthesis (6). In addition, a role for 1,25(OH)₂D₃ has been demonstrated in suppressing parathyroid cell proliferation in vitro (7), and in vivo in uremia-induced parathyroid hyperplasia (8). Although treatment with active vitamin D metabolites suppresses PTH secretion and prevents parathyroid hyperplasia in the majority of dialyzed patients, parathyroidectomy is still required in those cases with severe HPTH and osteitis fibrosa (9-10).

In clinical practice, parathyroidectomy is indicated if markedly elevated PTH levels are associated with one or more of the following: severe hypercalcemia; progressive and debilitating hyperparathyroid bone disease, often accompanied by bone pain; unexplained symptomatic myopathy; pruritus that does not respond to medical or dialytic therapy; progressive extraskeletal calcification or calcific uremic arteriolopathy with ischemic ulcers and necrosis. The latter is usually associated with hyperphosphatemia refractory to oral phosphate binders, because of PTH-induced phosphate release from bone (11).

It is important to appreciate that many of these problems can develop in dialysis patients without signifi-
Treatment of post-parathyroidectomy hypocalcemia

Mechanisms and clinical features of post-parathyroidectomy hypocalcemia

Hypocalcemia occurs when there is an inappropriate compensation or even a failure of the PTH-controlled homeostatic mechanisms that protect against a hypocalcemic stimulus. Therefore, hypocalcemia is a common, expected and sometimes dangerous parathyroidectomy complication (13), because of the concomitant drop in PTH levels and the increased shift of calcium from the circulation to the bone tissues. Post-surgical hypoparathyroidism, transient or permanent, can develop after neck surgery for thyroid disease because of inadvertent removal of, or trauma to, the parathyroid glands or their vascular supply. Neck exploration for primary HPTH is now the most frequent situation in which post-surgical hypoparathyroidism occurs. Frequently, severe and prolonged hypocalcemia develops after extensive parathyroid surgery, especially in patients with secondary HPTH with more severe bone disease before surgery. In parathyroidectomized patients, hypocalcemia results from the suddenly reduced PTH action on bone, which in more extreme cases presents as the “hungry bone” syndrome (14). Hyper-functioning tissue removal in either parathyroid adenoma or hyperplasia and suppression of the remaining parathyroid tissue by extensive manipulation of the parathyroid glands during surgery are post-operative complications that can contribute in reducing PTH secretion. In addition, the “hungry bone” syndrome is characterized by an intense recalcification of demineralized bone, a consequence of pre-operative bone disease (15). Basically, the mechanisms of hypocalcemia are the same in primary and secondary HPTH, but the extent of hypocalcemia is more pronounced in patients with renal failure.

Increased neuromuscular excitability causes the clinical manifestations of hypocalcemia. Table I summarizes the major signs and symptoms of hypocalcemia. These clinical features strictly relate to serum ionized calcium levels. In order to avoid clinical manifestations of hypocalcemia, serum calcium monitoring and preventive treatment is mandatory.

In addition, recent studies (13, 16-18) in patients with primary HPTH reported the need to evaluate serum calcium levels for predicting post-parathyroidectomy hypoparathyroidism and/or hypocalcemia. Bentrem et al (16) demonstrated that ionized calcium level measurement 16 hr post-surgery was sufficient to identify hypoparathyroidism in most patients. Both Moore et al (13) and Adams et al (17) proposed a model based on the slope between the first two serum calcium level determinations. Patients who develop hypocalcemia have a more negative slope than those remaining normocalcemic.
However, the prevalence of post-surgery hypocalcemia in patients with primary HPTH reported by these studies is rather low, ranging from 13 to 30%. In severe secondary HPTH, most patients need calcium supplements to avoid hypocalcemia. McHenry et al (10) demonstrated that 95% of renal patients, compared to 4% of patients with primary HPTH, developed hypocalcemia requiring intravenous (i.v.) calcium. Therefore, suggestions derived from studies on primary HPTH might not apply to ESRD patients.

In renal patients, careful plasma calcium monitoring is required. The nadir of the serum calcium level is seen, generally, 2-4 days post-surgery (19). Therefore, serum calcium levels should be measured 1-4x/day for the first few post-operative days. The K/DOQI guidelines suggest that the blood level of ionized calcium should be measured every 4-6 hr for the first 48-72hr post-surgery, and then 2x/day until stable (12). Some authors (20) recommend even stricter serum calcium monitoring (every 4hr for the first 2-3 days, and then every 12hr until serum calcium stabilizes), but in our experience this is rarely necessary.

**Treatment of post-parathyroidectomy hypocalcemia**

Calcium salts and vitamin D administration are common hypocalcemia treatments due to hyperplastic parathyroid gland removal. Treatment of post-parathyroidectomy hypocalcemia differs depending on the clinical setting: emergency, intermediate and maintenance (Tab. II).

Vitamin D metabolites are used to increase intestinal calcium absorption. Usually, calcitriol is the preferred vitamin D preparation because of its rather short half-life and the easy reversibility of side-effects. In addition, many calcium preparations can be used to prevent and treat post-parathyroidectomy hypocalcemia: Table III shows the most common calcium salts.

Immediately post-surgery, treatment should aim to adjust the elemental calcium dosage in order to keep the patient asymptomatic, with serum calcium >7.5 mg/dL. Chronic therapy should keep serum calcium levels to 8.4-9.6 mg/dL. Both prevention and treatment of symptomatic hypocalcemia are mandatory post-parathyroidectomy.

**Oral calcium**

In ESRD patients, post-parathyroidectomy 2-6 g/day (50-150 mmol) of oral elemental calcium supplementation should be used as soon as patients are able to swallow. K/DOQI guidelines suggest calcium carbonate use 1-2 g 3x/day (12). In patients with hyperphosphatemia, calcium is usually administered with meals to improve phosphate binding. Post-parathyroidectomy it could be better to administer calcium salts between meals, so that more calcium and phosphate can be absorbed.

**Intravenous calcium**

Calcium is usually administered intravenously in two circumstances: (a) rapid and progressive fall in plasma calcium levels (total calcium <7.2 mg/dL or 1.8 mmol/L; ionized calcium <0.9 mmol/L); (b) development of hypocalcemic symptoms (Tab. I). However, considering that most patients are hypercalcemic pre-surgery, if calcium levels are clearly and steeply declining, calcium infusion can be started earlier to pre-

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**TABLE I - SIGNS AND SYMPTOMS OF HYPOCALCEMIA**

<table>
<thead>
<tr>
<th>Neurumotorial</th>
<th>Paresthesias: mouth and extremities</th>
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<tbody>
<tr>
<td></td>
<td>Muscle spasms</td>
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<tr>
<td></td>
<td>Chvostek’s sign</td>
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<td></td>
<td>Trousseau’s sign</td>
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<td>Seizures</td>
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<td>Cardiac</td>
<td>EKG abnormalities</td>
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<td>Arrhythmia</td>
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<td></td>
<td>Hypotension</td>
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<td></td>
<td>Heart failure</td>
</tr>
</tbody>
</table>

**TABLE II - TREATMENT OF POST-PARATHYROIDECTOMY HYPOCALCEMIA**

| Emergency | • 20-30 mL of 10% Ca gluconate i.v. (100 mL dextrose 5% in solution) in 10-15’ |
| Intermediate | • Titrate plasma calcium toward normal values every 6-12hr with 900mg elemental calcium (100 mL of 10% Ca gluconate and 150 mL dextrose 5% in solution; administered with volumetric pump; starting infusion rate 20-30 mL/hr) |
| Maintenance | • Start oral calcium and vitamin D as soon as possible |
|            | • Oral calcium (usually up to 4 g/day) |
|            | • Vitamin D (calcitriol, up to 4 µg/day) |
|            | • Monitor serum calcium and magnesium |
|            | • Avoid phosphate depletion |
vent symptomatic hypocalcemia. Table II illustrates the practical approach to i.v. calcium infusion. The proposed starting dose corresponds to a rate of 1-2 mg/kg/hr of elemental calcium, in keeping with the K/DOQI guidelines (12). Calcium infusion should be reduced gradually maintaining the ionized calcium level within the normal range.

Recently, Nakagawa et al. (21) demonstrated in 49 patients with secondary HPTH that the amount of calcium supplementation for the first 48 hr after total parathyroidectomy with subcutaneous auto-transplantation is related to pre-operative intact PTH levels and serum alkaline phosphatase. Therefore, if these two parameters are highly elevated, as is often the case in renal patients pre-parathyroidectomy, the necessity of i.v. calcium infusion is predictable in most patients.

Magnesium and phosphate

Magnesium and phosphate supplementation has been suggested for patients with normal renal function post-parathyroidectomy for primary HPTH. Indeed, even chronic kidney disease patients with hypocalcemia and hypomagnesemia may not respond to calcium replacement alone (22). Therefore, if serum magnesium levels are low, they require correction. Some patients require phosphate supplements (12). Phosphate replacement should be performed with caution, being reserved for patients with very severe hypophosphatemia (<1 mg/dL). Oral phosphate supplements could bind with calcium in the gastrointestinal tract and further worsen the underlying hypocalcemia. Therefore, phosphate supplements must not be taken with meals or close to calcium salt administration.

In patients with chronic renal failure, both hypomagnesemia and hypophosphatemia are uncommon. Although parathyroidectomy leads to a rapid reduction in the plasma phosphate concentration, the value falls from an initially high level to one that usually remains above the normal range. However, it is advisable to monitor serum phosphate and magnesium levels. In addition, if the patient receives phosphate binders pre-surgery, this therapy may need to be discontinued or reduced as dictated by serum phosphorus levels (12).

Vitamin D administration

In parathyroidectomized dialysis patients, calcitriol administration seems to be useful (23-26). In a randomized controlled double-blind trial, Clair et al. (24) compared vitamin D and calcium supplementation efficacy during the post-parathyroidectomy period (days 1-14) to calcium supplementation alone. From day 1 post-surgery, seven uremic patients were treated with oral calcitriol (up to 4 µg/day) plus calcium, and the remaining seven with a placebo and calcium. Post-operative oral calcitriol ameliorated the mean reduction of serum calcium levels (0.25 ± 0.06 mM) compared to placebo-treated patients (0.45 ± 0.05 mM, p<0.05). In addition, vitamin D-treated uremic patients required less calcium supplementation compared to those receiving a placebo (24). Mazzaferro et al. (25) also demonstrated that in dialysis patients immediately post-parathyroidectomy calcitriol treatment barely affected bone turnover, but improved hypocalcemia through its effect on intestinal calcium absorption. These authors also showed that in the first 10 days post-surgery the average administered calcitriol dosage was 2.4 ± 1.0 µg/day, and total calcium dosages, administered i.v. and orally, were 559 ± 485 mg and 16.9 ± 5.7 g respectively. With this treatment,

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**TABLE III - COMMON CALCIUM PREPARATIONS USED IN CLINICAL PRACTICE**

<table>
<thead>
<tr>
<th>Calcium preparation</th>
<th>1g of the Ca preparation provides elemental Ca</th>
<th>Grams necessary to provide 1g of elemental calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium acetate (25% elemental Ca)</td>
<td>250 mg</td>
<td>4.0</td>
</tr>
<tr>
<td>Calcium carbonate (40% elemental Ca)</td>
<td>400 mg</td>
<td>2.5</td>
</tr>
<tr>
<td>Calcium chloride (27% elemental Ca)</td>
<td>270 mg*</td>
<td>3.7</td>
</tr>
<tr>
<td>Calcium gluconate (9% elemental Ca)</td>
<td>90 mg**</td>
<td>11.1</td>
</tr>
</tbody>
</table>

* 10 mL of 10% CaCl for i.v. administration contains 270 mg of elemental calcium

** 10 mL of 10% Ca gluconate for i.v. administration contains 90 mg of elemental calcium
plasma calcium levels fell from 10.1 to 7.7 mg/dL, but the patients remained asymptomatic. Although no studies have addressed i.v. calcitriol use in post-parathyroidectomy hypocalcemia management, it could be useful post-operatively, when oral administration is not feasible.

**Dialysis**

Dialysis could be another method of treating post-parathyroidectomy hypocalcemia, although dialysis per se should only be considered as an ancillary tool. Increasing calcium concentration in the dialysis bath can ameliorate the severity of hypocalcemia. If a high calcium concentration dialysis bath is not available, i.v. calcium can be infused during dialysis. In patients on peritoneal dialysis, continuous ambulatory intraperitoneal calcium therapy, 1-3 vials of calcium gluconate added to each bag of peritoneal dialysate, has been proposed as post-parathyroidectomy hypocalcemia treatment (26).

**Conclusions**

In ESRD patients, secondary HPTH is a frequent complication. Tertiary HPTH is the clinical condition in which treatment with vitamin D and phosphate binders are not capable of reducing PTH secretion. In these cases, parathyroidectomy is often necessary. Post-parathyroidectomy hypocalcemia is a common complication, which can be preventable and treated with calcium supplementation and/or active vitamin D metabolites. Daily follow-up of both serum calcium and phosphorus are mandatory in preventing this major post-operative complication. Based on the available evidence and on common sense clinical practice, we propose a protocol for the prevention and treatment of post-parathyroidectomy hypocalcemia, illustrated in Figure 1 by a clinical algorithm.

In choosing a treatment for post-parathyroidectomy hypocalcemia, many questions remain unanswered. Since many variables (total vs. subtotal parathyroidectomy, i.v. calcium use and early calcitriol use) can
modulate the effect of surgery on plasma calcium levels, treatment is often individualized. Although managing hypocalcemia is a common problem, data from controlled trials are scarce or incomplete. In particular, a clinical protocol for calcium administration in ESRD patients undergoing parathyroidectomy has not been established. The reasonable length of hospitalization, which is longer than in patients with primary HPTH, the correct frequency of plasma calcium determinations, the usefulness of total vs. ionized calcium, and correct vitamin D metabolite use, are the major points to clarify in the follow-up of parathyroidectomy.

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