Teriparatide Therapy and Reduced Postoperative Hospitalization for Postsurgical Hypoparathyroidism

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IMPORTANCE Up to 20% of patients undergoing thyroidectomy develop hypocalcemia after surgery. Although usually transient, severe symptomatic hypocalcemia may occur. Teriparatide acetate (recombinant human parathyroid hormone 1-34) therapy can rapidly raise calcium levels.

OBJECTIVE To test the hypothesis that teriparatide therapy in patients with postthyroidectomy hypoparathyroidism would expedite relief of symptomatic hypocalcemia and reduce the duration of hospitalization compared with standard treatment.

DESIGN, SETTING, AND PARTICIPANTS Case series of all hospitalized patients 18 years or older treated with teriparatide for symptomatic postthyroidectomy hypocalcemia occurring immediately after thyroidectomy at Mayo Clinic, Rochester, Minnesota, between January 1, 2008, and June 30, 2014. A secondary analysis was performed with matched control and cohort groups having postthyroidectomy hypocalcemia of similar degree who received standard treatment only. Participants included 8 hospitalized patients who received teriparatide therapy after 24 hours of standard treatment (cases) and eight control patients selected from a cohort of 1193 thyroidectomies were matched for age, sex, body mass index, and nadir calcium levels.

INTERVENTION Teriparatide acetate therapy (20 μg twice daily) subcutaneously for 1 week, with the option of continuing at 20 μg/d for up to 3 weeks.

MAIN OUTCOMES AND MEASURES Safety, symptom resolution, calcium supplementation, and duration of hospitalization.

RESULTS Among the 16 case and control patients the median nadir calcium level was 7.1 mg/dL in both groups. Most patients underwent thyroidectomy for thyroid cancer. Teriparatide therapy was safe, with no adverse events noted, and completely eliminated symptomatic hypocalcemia in all treated patients within 24 hours of initiation. Hospital discharge occurred at a median of 1.0 day (interquartile range, 1.0-1.0 day) after teriparatide therapy initiation among cases vs 2.5 days (interquartile range, 1.8-3.0 days) after the equivalent clinical point was reached in controls (P = .01). This value was 2.0 days in the source cohort (P = .02). On hospital discharge, patients had similar calcium levels. Six months after surgery, all patients treated with teriparatide showed partial or complete parathyroid recovery. Calcium supplementation and calcium levels were comparable between the groups.

CONCLUSIONS AND RELEVANCE In this pilot study, teriparatide therapy in patients with postthyroidectomy hypoparathyroidism was safe, rapidly eliminated hypocalcemic symptoms, and likely reduced the duration of hospitalization. Given the limitations of this small study, a large-scale randomized trial is needed to verify these results and to assess the long-term effect of teriparatide therapy on clinical outcomes.
Postoperative hypoparathyroidism that leads to hypocalcemia occurs in up to 20% of patients who undergo total thyroidectomy.\textsuperscript{1-3} While hypocalcemia is transient in most patients after thyroidectomy, reported rates of permanent hypocalcemia range from 0.8% to 8.3%.\textsuperscript{4-6} When severe, hypocalcemia can result in cardiac arrhythmias and tetany, increased morbidity, prolonged duration of hospitalization, and death. Parathyroid gland injury, including devascularization or removal of 1 or more parathyroid glands during surgery, is the most common cause of postoperative hypocalcemia.\textsuperscript{7,8} Other factors that can influence the relative likelihood and degree of hypocalcemia include vitamin D deficiency, age, and the presence of hungry bone syndrome.\textsuperscript{7,9}

Hypoparathyroidism remains one of the few hormonal insufficiency disorders in which replacement of the absent hormone is not considered the standard of care. Accordingly, treatment of hypocalcemia has historically included the use of calcium and vitamin D supplementation to maintain calcium levels within the low normal range. Thiazide diuretics are frequently used in conjunction with calcium and vitamin D supplementation to enhance distal renal tubular calcium reabsorption and thereby raise calcium levels. However, promptly correcting and maintaining calcium levels in a desirable range can be challenging in clinical practice.\textsuperscript{9,10}

Studies\textsuperscript{11,12} have demonstrated that teriparatide acetate (recombinant human parathyroid hormone [PTH] 1-34) therapy can successfully treat patients with chronic hypoparathyroidism, and lead to maintenance of normocalcemia and reduction in hypercalcuria compared with calcium and calcitriol standard treatment. However, little information exists regarding the usefulness of teriparatide therapy to rapidly elevate calcium levels, alleviate symptoms, and limit the risk of hypocalcemia-associated complications in patients with postsurgical hypoparathyroidism that develops immediately after thyroidectomy.

Accordingly, the objective of this pilot study was to describe the clinical course of postsurgical hypoparathyroidism occurring immediately after thyroid surgery in a series of patients treated with teriparatide, as well as the safety of this approach. We hypothesized that teriparatide therapy in patients with postthyroidectomy hypoparathyroidism would expedite relief of symptomatic hypocalcemia and reduce the duration of hospitalization compared with standard treatment.

Methods

We report herein a case series from Mayo Clinic, Rochester, Minnesota, of all patients treated with teriparatide between January 1, 2008, and June 30, 2014, for symptomatic hypocalcemia occurring immediately after thyroidectomy in the hospital setting. The initial 3 patients were treated based on a clinical protocol from October 1, 2008, until January 31, 2010, at which time a Mayo Clinic Institutional Review Board–approved protocol was developed and implemented with all subsequent patients treated after written informed consent was obtained. All patients described herein agreed to have their medical records reviewed for research purposes, in compliance with Minnesota statutes, and data on all patients were collected based on the approved protocol.

Targeted patients were hospitalized individuals who developed hypocalcemia in the immediate postoperative period following total thyroidectomy. Patients were considered for teriparatide therapy if there was evidence from the operative report and the pathology report of preserved parathyroid tissue such that they were not deemed to have permanent hypoparathyroidism. Included patients were identified by their surgical teams (G.B.T., M.L.R., and J.L.K.) because of persistent hypocalcemia incompletely responsive to standard treatment with calcium and calcitriol. Potential study patients were presented with the option of teriparatide therapy if they had symptomatic hypocalcemia, with a total serum calcium level of less than 8.0 mg/dL (to convert calcium level to millimoles per liter, multiply by 0.25) persisting after 24 hours of standard treatment with calcitriol (minimum, 0.25 μg twice daily) and calcium supplementation (minimum, 1.5 g/d of elemental calcium).

Exclusion criteria were applied. Patients with the following characteristics were excluded from the study: age younger than 18 years or the presence of renal failure, any prior parathyroid pathology, preexisting hypercalcemia, metabolic bone diseases other than osteoporosis, ongoing teriparatide therapy for osteoporosis, active nonthyroidal malignancy or suspicion of significant residual thyroid malignancy, history of skeletal malignancies (primary or metastatic), pregnancy, active or recent urolithiasis, digitalis therapy, increased baseline risk of osteosarcoma (ie, family history of osteosarcoma or prior radiation therapy involving the skeleton), or an unexplained elevation of serum alkaline phosphatase levels.

Patients were contacted directly in the hospital regarding study participation. They were offered treatment protocols for the inpatient and outpatient stages. For the inpatient stage, the protocol included teriparatide acetate therapy (initiated at 20 μg twice daily) subcutaneously using an injection pen (Forteo; Eli Lilly and Company) and continued at this dose for 1 week, with the option of continuing at 20 μg/d for 3 weeks in total. Patients were monitored for transient episodes of symptomatic orthostatic hypotension (reported to occur infrequently following the first doses of teriparatide). Serum calcium levels were measured every 12 hours. Serum magnesium and 25-hydroxyvitamin D levels were measured, and replacement was administered as indicated. For our analysis, individuals were considered ready for hospital discharge when calcium levels exceeded 7.5 mg/dL and increased over 12 hours in an asymptomatic patient receiving stable therapy without the need for intravenous calcium administration in the preceding 24 hours. This point was considered the hospital discharge time, despite some patients requiring additional time because of hospital discharge logistics unrelated to calcium level. Patients and family members were instructed on teriparatide acetate administration and were discharged with possession of the FORTEO pen used up to that point, which contained the remainder of the 28 doses of 20 μg. Patients were asked to telephone the study coordinator or the principal investigator (M.N.S.) if symptoms of hypocalcemia developed.

For the outpatient stage, the protocol required the serum calcium level to be measured 48 hours after hospital discharge or if the patient manifested symptomatic hypocalcemia. At the con-
conclusion of the first week of teriparatide therapy, patients discontinued teriparatide for 24 hours before measurement of serum calcium, phosphorus, and PTH levels. If hypocalcemia persisted, patients continued teriparatide acetate therapy at 20 μg once daily for the next day. The 3 patients who received teriparatide therapy before implementation of the institutional review board protocol discontinued teriparatide on hospital discharge. At the conclusion of the second week, teriparatide therapy was again discontinued for 24 hours, and calcium, phosphorus, and PTH levels were measured. If the calcium level was less than 8.0 mg/dL, teriparatide acetate therapy was resumed at 20 μg/d, and laboratory assessments were repeated 1 week later. Periodic telephone communication was used to discuss the results and to identify symptomatic hypocalcemia. After the third week of treatment, teriparatide therapy was discontinued because the maximum number of 28 doses available in each pen was completed. If the serum calcium level remained less than 8.0 mg/dL after the third week of teriparatide therapy, patient management was continued per current standard treatment for hypoparathyroidism. Concomitant calcium and calcitriol (with or without hydrochlorothiazide) were used throughout the teriparatide therapy period as per current clinical standards.8

To assess teriparatide efficacy, a group of control subjects was identified from a cohort of Mayo Clinic patients in Rochester who developed postsurgical hypoparathyroidism between January 1, 2004, and January 31, 2010. Controls were matched for age, sex, body mass index, and nadir serum calcium levels with patients treated with teriparatide, and all received standard treatment for hypocalcemia (ie, calcium and calcitriol supplementation with or without hydrochlorothiazide therapy). These matching variables are known to influence gastrointestinal transit time, nutrient absorption, and renal excretion and thus calcium and vitamin D stores and metabolism. We also expected that age, sex, and nadir calcium level might influence hypocalcemia symptoms. Given potential limitations associated with the matched historical controls, we also extracted data regarding the duration of hospitalization for the entire patient cohort meeting the listed criteria that served as the source of the 8 matched controls. To compare the results of teriparatide therapy, the starting point for the assessment of controls was similar to that of cases (ie, symptomatic hypocalcemia persisting after 24 hours of standard treatment), henceforth referred to as the intervention time. We certify that this article complies with the principles of ethical publishing.

Matched pair analysis was performed to compare variables before and after the intervention between the teriparatide and control groups. The Wilcoxon rank sum nonparametric test was used for comparison of cases with controls. For categorical variables, χ² test was performed. Given the small size of the groups, data are expressed as the median (interquartile range [IQR]). Statistical significance was set at P < .05. Statistical analysis was performed using a software program (JMP, version 9; SAS Institute Inc).

Table 1. Baseline and Biochemical Characteristics of 8 Cases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>41 (31-53)</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>3:5</td>
</tr>
<tr>
<td>Body mass index, median (IQR)*</td>
<td>26.7 (24.3-28.7)</td>
</tr>
<tr>
<td>Nadir serum calcium level, median (IQR), mg/dL</td>
<td>7.1 (6.5-7.3)</td>
</tr>
<tr>
<td>Parathyroid recovery, partial or complete</td>
<td>8/8</td>
</tr>
<tr>
<td>On Hospital Discharge</td>
<td></td>
</tr>
<tr>
<td>Serum calcium level, median (IQR), mg/dL</td>
<td>8.7 (8.4-9.1)</td>
</tr>
<tr>
<td>Oral elemental calcium therapy, median (IQR), g</td>
<td>2.3 (1.9-4.1)</td>
</tr>
<tr>
<td>Calcitriol therapy, median (IQR), μg</td>
<td>0.75 (0.31-1.00)</td>
</tr>
<tr>
<td>Hydrochlorothiazide therapy</td>
<td>3/8</td>
</tr>
<tr>
<td>At 90 d After Surgery</td>
<td></td>
</tr>
<tr>
<td>Serum calcium level, median (IQR), mg/dL</td>
<td>8.9 (8.4-9.0)</td>
</tr>
<tr>
<td>Oral elemental calcium therapy, median (IQR), g</td>
<td>2.0 (1.3-2.2)</td>
</tr>
<tr>
<td>Calcitriol therapy, median (IQR), μg</td>
<td>0.25 (0.13-0.38)</td>
</tr>
<tr>
<td>Hydrochlorothiazide therapy</td>
<td>0/8</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

SI conversion factor: To convert calcium level to millimoles per liter, multiply by 2.496.

Results

Eight hospitalized patients received teriparatide therapy after 24 hours of standard treatment for severe hypocalcemia (Table 1). Patients were predominantly middle-aged (median age, 41 years), and 5 of 8 were female. The median body mass index (calculated as weight in kilograms divided by height in meters squared) was 32.5 (IQR 27.5-37.5 ng/mL) (to convert 25-hydroxyvitamin D level to nanomoles per liter, multiply by 2.496).

All cases were symptomatic at the time of teriparatide therapy consideration, with manifestations including Chvostek sign (mild), fingertip or perioral paresthesia (moderate), or QT prolongation (severe). The treatments they were receiving at that point included calcium supplementation (>3.0 g of elemental calcium in 7 cases), calcitriol (median, 1.00 μg; IQR, 0.81-1.00), and hydrochlorothiazide in 5 of 8 cases. Intravenous calcium was administered in 4 cases via peripherally inserted central catheter or central line.

The period from surgery to the intervention time was a median of 3.0 (IQR, 2.0-4.0) days. At that point, the nadir calcium level was less than 7.3 mg/dL in most patients. Teriparatide therapy was initiated by a nurse who then trained patients on teriparatide administration, with all cases able to self-administer the medication by the time of hospital discharge.

Teriparatide Therapy

After the first teriparatide dose, serum calcium levels increased in all cases, and all became asymptomatic within the first 24 hours of treatment initiation. Accordingly, cases were ready for hospital discharge at a median of 1.0 day (IQR, 1.0-1.0 day) after teriparatide therapy initiation. During the intervention period, there was a decline in daily calcium supplementation (from 4300 to 2400
mg) and a lower requirement for intravenous calcium therapy (required by 4 patients before the intervention vs by 2 patients during the intervention). On hospital discharge, patients treated with teriparatide had a median calcium level of 8.7 mg/dL (8.4-9.1 mg/dL) (Table 1). The overall duration of teriparatide therapy varied: 3 patients received teriparatide for 1 week, 4 patients required teriparatide for 2 weeks, and 1 patient continued a teriparatide regimen for 3 weeks. During teriparatide therapy, all patients remained asymptomatic. Calcium and PTH levels determined at days 9 and 17 aided in decision making related to adjustment of calcium and calcitriol therapy, as well as in determining the duration of teriparatide therapy. Discontinuation of teriparatide therapy occurred based on evidence of parathyroid gland recovery, completion of 28 doses, or patient preference. While all cases started therapy with undetectable PTH levels, levels became detectable by 90 days after surgery in all patients treated with teriparatide. No adverse events were associated with teriparatide therapy.

**Case-Control Analysis**

Eight matched controls were identified (Table 2). Most controls (7 of 8) underwent surgery for thyroid cancer (P = .35). In 5 controls, no parathyroid gland was removed, and 1 control each had 1 gland, 2 glands, and 3 glands removed, respectively. No controls underwent parathyroid autotransplantation. At the intervention time, all controls were symptomatic and receiving calcium (>3.0 g/d of elemental calcium in 6 patients) and calcitriol. Calcitriol therapy (median, 0.50 μg/d; IQR, 0.06-0.69 μg/d) was less aggressive than for cases (P = .004). Two controls also received hydrochlorothiazide, and 3 controls required intravenous calcium administration. The median period from surgery to the intervention time was 2.0 days (IQR, 2.0-2.8 days) and was similar to that in cases (P = .18). At the intervention time, calcium supplementation and calcium levels were comparable between the groups.

From the intervention time onward, symptomatic hypocalcemia persisted for a median of 48 hours (range, 42-48 hours) in controls, in contrast to cases. Similarly, controls remained hospitalized for an additional median of 2.5 days (IQR, 1.8-3.0 days) after the intervention time was reached with a median of 1.0 day (IQR, 1.0-1.0 day) among cases (P = .01) (Figure). While cases and controls received similar amounts of oral calcium and calcitriol therapy following the intervention time, there was a statistically nonsignificant suggestion of a higher intravenous calcium requirement in controls (5 of 8 in controls vs 2 of 8 in cases, P = .13) (Table 3). Compared with cases, controls were discharged with similar calcium and calcitriol supplementation doses and had similar median calcium levels (8.3 mg/dL in controls vs 8.7 mg/dL in cases, P = .10).

**Cohort Analysis**

To document the validity of the matched control cohort, we collected hospitalization data for the entire cohort from which controls were selected. Collectively, 1193 thyroidectomies were performed during the study period, with 85 patients developing hypocalcemia of less than 8.0 mg/dL persisting longer than 24 hours. Despite medical therapy, 40 patients remained symptomatic and would have qualified for the teriparatide therapy protocol. The median duration of hospitalization in these 40 patients after the intervention time was 2.0 days (IQR, 1.1-3.5 days).
Collectively, these benefits are likely to translate to a significant reduction in the overall costs sufficient to compensate for the cost of teriparatide therapy (approximately $1050 for a 21-day regimen at the time of the intervention). To render this parameter independent of administrative factors, we used a clinical and biochemical definition to determine when patients could be safely discharged from the perspective of their calcium levels. An inherent limitation of our study is the comparison with retrospectively matched controls. Therefore, we sought to compare our cases with the entire cohort from which the matched controls were drawn, and we found similar results. Unfortunately, there is scant literature describing hospitalization in similar patients with hypocalcemia, and no defined standards exist for determining when such patients can be safely discharged, to our knowledge.

Baseline calcitriol supplementation differed significantly between the groups, with cases receiving more aggressive supplementation than controls. Thereafter, during the intervention period and on hospital discharge, the groups were similar regarding calcium and calcitriol therapy. Thus, it is unlikely that baseline calcitriol therapy had a meaningful effect on the decreased duration of hospitalization that was observed with teriparatide therapy. This finding, which likely reflects a variation in clinical practice, underscores the limitations of case-control studies.

Teriparatide has a mechanism of action similar to that of endogenous PTH and increases serum calcium levels by enhancing gastrointestinal calcium absorption and decreasing renal calcium excretion. It has been used for PTH therapy in patients with chronic hypoparathyroidism, with twice daily dosing proving superior to once daily dosing because of diminished fluctuations in serum calcium levels and less hypercalciuria. Limited data exist on the efficacy of teriparatide therapy for the management of hypoparathyroidism in the immediate postoperative setting. However, Hu et al. found that teriparatide acetate therapy at a dose of 40 μg twice daily normalized serum calcium levels within 24 hours more effectively than 20 μg twice daily, without leading to hypercalcemia or other adverse events in the short term. The long-term safety of teriparatide therapy remains a potential concern because of reports from early animal investigations that noted an increased risk of osteosarcoma in rats treated with teriparatide. However, teriparatide therapy for up to 3 years in human studies was not associated with safety concerns, and our short-term intervention protocol is likely to raise such issues.

Given the limited duration of teriparatide therapy and the short subsequent outpatient follow-up in our study, our data...
did not allow us to determine whether teriparatide therapy affects the risk of permanent hypoparathyroidism. However, at least within the first 3 months after the intervention, there was no evidence of a negative effect of teriparatide therapy on the recovery of parathyroid function, with all 8 patients treated with teriparatide demonstrating at least partial (if not complete) regained parathyroid gland function.

Our study has several limitations. Chief among these considerations is the small sample size, including the caveat that 3 patients in the teriparatide group were not part of the institutional review board–approved treatment protocol; therefore, inconsistencies exist in their treatment plan. Another limitation is the case-control format we used to determine the effect of teriparatide therapy on the duration of hospitalization. Because controls were identified from a retrospective cohort, they are subject to the usual potential biases that exist in such studies. In addition, historical controls lacked some biochemical variables (eg, 25-hydroxyvitamin D levels). While we attempted to compensate for this by matching, it remains possible that controls had lower vitamin D stores, which could have prolonged the recovery from hypocalcemia and increased the duration of hospitalization. To minimize potential differences, we included controls from a period partially overlapping that of the included cases. Because no major changes occurred in the routine clinical management of postoperative hypoparathyroidism during this time, we believe that historical bias was minimized but not eliminated and thus should be considered in the interpretation of our results. Finally, it is possible that patients treated with teriparatide received more aggressive standard treatment for hypocalcemia, as suggested by calcitriol use at the intervention time as noted above in the Case-Control Analysis subsection of the Results section.

Conclusions

In this small pilot study, we found that teriparatide therapy in hospitalized patients immediately following thyroidectomy complicated by hypoparathyroidism was safe, rapidly eliminated hypocalcemic symptoms, and was likely associated with reduced duration of hospitalization. Given the limitations of our study, these provocative results will require validation, ideally in a multicenter randomized clinical trial, before they can be translated into practice. While our data suggest that such a trial would be safe, it should also be designed to assess the long-term effect of teriparatide therapy on all clinical outcomes.

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Study concept and design: Bancos, Thompson, Kasperbauer, Clarke, Drake, Stan.

Acquisition, analysis, or interpretation of data: Shah, Bancos, Richards, Kasperbauer, Clarke, Drake, Stan.

Drafting of the manuscript: Shah, Drake, Stan.

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Study supervision: Richards, Kasperbauer, Drake, Stan.

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REFERENCES


