

Prospective Study of Perioperative Factors Predicting Hypocalcemia After Thyroid and Parathyroid Surgery

Stanley H. Chia, MD; Robert A. Weisman, MD; David Tieu, BS; Colleen Kelly, PhD; Wolfgang H. Dillmann, MD; Lisa A. Orloff, MD

Objective: To identify whether perioperative 1,25-dihydroxyvitamin D or parathyroid hormone (PTH) levels will predict the development of hypocalcemia after thyroid and parathyroid surgery.

Design: Prospective study.

Setting: University hospital.

Patients: The study included 103 patients who underwent thyroid or parathyroid surgery between 2002 and 2004, with a comparison of the patients who underwent thyroid lobectomy (TL; n=34), total thyroidectomy (TT; n=27), parathyroid adenoma excision (PAE; n=34), and subtotal parathyroidectomy for hyperplasia (SP; n=8).

Main Outcome Measures: Preoperative 1,25-dihydroxyvitamin D levels, number of patients requiring calcium replacement, and postoperative PTH and calcium levels.

Results: No patients in the TL or PAE group developed postoperative hypocalcemia that required calcium replacement. Six patients (22%) in the TT group and 3 patients (38%) in the SP group required calcium replacement for clinically significant hypocalcemia ($P<.001$).

All patients who required calcium replacement had PTH levels of less than 15 pg/mL (1.6 pmol/L) 8 hours after surgery. Among the patients with postoperative PTH levels of less than 15 pg/mL (1.6 pmol/L) 8 hours after surgery, no patients in the PAE group required calcium replacement, compared with 75% of patients in the TT and SP groups ($P<.001$). The patients in the TT group had significantly lower postoperative calcium levels than those in the TL ($P<.001$) or the PAE ($P<.005$) group. The patients in the TL group reached stable calcium levels significantly earlier than those in the other groups (15.8 hours after surgery; $P<.05$). There was no relationship between preoperative 1,25-dihydroxyvitamin D levels and postoperative calcium levels.

Conclusions: Preoperative 1,25-dihydroxyvitamin D levels were not predictive of postoperative calcium levels. Patients who undergo PAE or TL are at extremely low risk for requiring calcium replacement. Patients who undergo TT or SP with 8-hour postoperative PTH levels greater than or equal to 15 pg/mL (1.6 pmol/L) are at low risk for developing postoperative hypocalcemia, whereas those with PTH levels less than 15 pg/mL (1.6 pmol/L) have a high risk of developing hypocalcemia.

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Author Affiliations: Divisions of Head and Neck Surgery (Drs Chia and Weisman and Mr Tieu) and Endocrinology and Metabolism (Dr Dillmann), University of California, San Diego; Department of Mathematics and Statistics, San Diego State University (Dr Kelly); and Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco (Dr Orloff).

HYPOCALCEMIA IS A POTENTIAL problem in the early period after thyroid and parathyroid surgery. Patients who undergo thyroidectomy or parathyroidectomy have traditionally been admitted for observation after surgery, with monitoring of calcium levels until they stabilize. Recently, there has been interest in identifying factors that can reliably predict the development of postoperative hypocalcemia after thyroid and parathyroid surgery. The ability to consistently identify those patients who are at risk for developing hypocalcemia could enable surgeons to select patients who can undergo these procedures on an outpatient or

a short-stay basis. Performing these surgical procedures on an outpatient basis could result in a cost reduction of as much as 50% compared with traditional postoperative hospital stays.¹

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Our study objectives were to prospectively evaluate patients undergoing thyroid and parathyroid surgery and to determine whether preoperative 1,25-dihydroxyvitamin D levels or postoperative parathyroid hormone (PTH) levels could reliably predict the development of postoperative hypocalcemia.

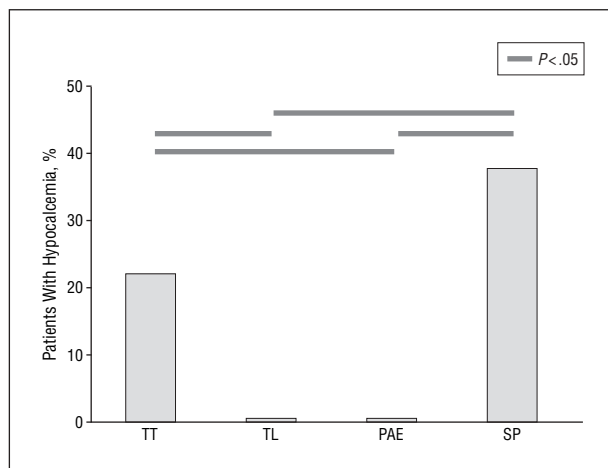


Figure 1. Percentage of patients developing hypocalcemia by group. No patients in the thyroid lobectomy (TL) or the parathyroid adenoma excision (PAE) group developed hypocalcemia. Significant differences between groups are indicated by bars at the top of the graph. TT indicates total thyroidectomy; SP, subtotal parathyroidectomy for hyperplasia.

METHODS

Approval for this study was granted by the institutional review board of the University of California, San Diego. Patients undergoing thyroid or parathyroid surgery between 2002 and 2004 at the University of California, San Diego, were entered into a clinical trial during which laboratory and clinical data were collected prospectively. Preoperative 1,25-dihydroxyvitamin D levels were obtained, and intact PTH levels were drawn 8 hours after the completion of surgery. Calcium levels were measured 8 hours after the completion of surgery, and then every 8 hours until the levels stabilized. Serum calcium, intact PTH, and serum 1,25-dihydroxyvitamin D levels were measured 1 week after surgery.

The patients were separated into the following 4 groups by the procedure performed: total thyroidectomy (TT), thyroid lobectomy (TL), parathyroid adenoma excision (PAE), and subtotal parathyroidectomy for hyperplasia (SP). All patients undergoing PAE had unilateral exploration except when no obvious adenoma was identified on the first side. Patients undergoing SP had 3½ glands removed, leaving the remaining half gland in situ, with its blood supply intact whenever possible. If the blood supply was compromised, the remaining gland was minced and implanted into the sternocleidomastoid or brachioradialis muscle.

The patients were monitored for postoperative hypocalcemia, which was defined as the development of symptoms of perioral or fingertip paresthesias or numbness, tetany, a newly positive Chvostek sign, or calcium levels less than or equal to 7.0 mg/dL (1.75 mmol/L). All patients who developed postoperative hypocalcemia were given intravenous calcium and calcitriol supplementation. The lowest postoperative calcium levels and time to reach lowest calcium levels were determined for each group. These values were correlated with preoperative 1,25-dihydroxyvitamin D and postoperative PTH levels and compared between groups.

All data are expressed as mean ± SD. Statistical comparisons of the rate of hypocalcemia between groups were performed using the Fisher exact test. Comparisons of the lowest calcium levels between groups were performed using a 1-way analysis of variance with Tukey post hoc analysis. Correlation of 1,25-dihydroxyvitamin D and PTH levels with postoperative calcium was performed using a generalized linear model.

Table. Patients With 8-Hour Postoperative Parathyroid Hormone Levels of Less Than 15 pg/mL (1.6 pmol/L) Separated by Group*

Group	Total No. of Patients	No. of Patients Developing Hypocalcemia	Patients Developing Hypocalcemia, %
Total thyroidectomy	8	6	75
Parathyroid adenoma excision	12	0	0
Subtotal parathyroidectomy for hyperplasia	4	3	75

*No patients in the parathyroid adenoma excision group developed hypocalcemia ($P < .05$ vs total thyroidectomy and subtotal parathyroidectomy groups). No patients undergoing thyroid lobectomy had 8-hour postoperative parathyroid hormone levels of less than 15 pg/mL (1.6 pmol/L).

RESULTS

A total of 103 patients were enrolled during the study period (2002-2004). Twenty-seven patients underwent TT, 34 patients underwent TL, 34 patients underwent PAE, and 8 patients underwent SP. The percentages of patients in each study group who developed postoperative hypocalcemia are shown in **Figure 1**. No patients in the TL or PAE groups developed hypocalcemia after surgery. In contrast, 6 (22%) of 27 patients in the TT group and 3 (38%) of 8 patients in the SP group developed hypocalcemia. Direct comparisons between groups demonstrated that the TL and PAE groups demonstrated significantly lower rates of hypocalcemia than the TT and SP groups ($P < .05$).

All patients who developed hypocalcemia were noted to have an 8-hour postoperative PTH level of less than 15 pg/mL (1.6 pmol/L) (**Table**). Interestingly, 12 of 34 patients in the PAE group had 8-hour postoperative PTH levels of less than 15 pg/mL (1.6 pmol/L), but none of them developed hypocalcemia. This result was statistically significant when compared with the TT ($P < .005$) and SP ($P < .05$) groups. In the TT group, 6 (75%) of 8 patients with PTH levels of less than 15 pg/mL (1.6 pmol/L) developed hypocalcemia. In the SP group, 3 (75%) of 4 patients with 8-hour postoperative PTH levels of less than 15 pg/mL (1.6 pmol/L) developed hypocalcemia. An 8-hour postoperative PTH value of less than 15 pg/mL (1.6 pmol/L) had 100% sensitivity and 90.5% specificity as a predictor of the development of postoperative hypocalcemia in the TT group and 100% sensitivity and 83.3% specificity in the SP group.

Among the patients with 8-hour postoperative PTH levels of less than 15 pg/mL (1.6 pmol/L), those in the TT group had the lowest levels of calcium after surgery (7.05 ± 0.05 mg/dL [1.76 ± 0.12 mmol/L]), followed by those in the SP group (7.85 ± 0.28 mg/dL [1.96 ± 0.07 mmol/L]) and those in the PAE group (8.48 ± 0.14 mg/dL [2.12 ± 0.04 mmol/L]). The results are summarized in **Figure 2**. The postoperative calcium nadir in the TT group was significantly less ($P < .05$) than that in the SP and PAE groups. The calcium nadir in the SP group was also significantly less than that in the PAE group ($P < .05$).

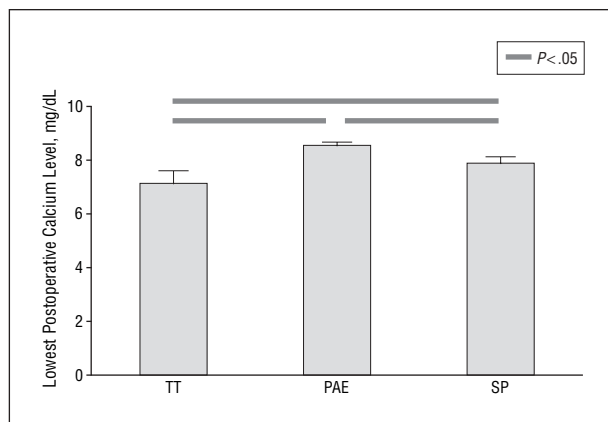


Figure 2. Lowest postoperative calcium levels in patients with 8-hour postoperative parathyroid hormone levels of less than 15 pg/mL (1.6 pmol/L). Patients in the total thyroidectomy (TT) group demonstrated the lowest postoperative calcium levels, followed by the patients who underwent subtotal parathyroidectomy for hyperplasia (SP) and those who underwent parathyroid adenoma excision (PAE). Significant differences between groups are noted by the bars at the top of the graph. The error bars refer to the SD of the mean for each group represented. To convert calcium values to millimoles per liter, multiply by 0.25.

Comparisons of the lowest postoperative calcium levels by group are seen in **Figure 3**. Patients who underwent TT had the lowest calcium level (7.73 ± 0.74 mg/dL [1.93 ± 0.18 mmol/L]), which was statistically significant when compared with patients who underwent TL ($P < .001$) and PAE ($P < .005$). The SP group had a postoperative calcium nadir of 8.15 ± 0.62 mg/dL (2.04 ± 0.16 mmol/L); the TL group, 8.29 ± 0.35 mg/dL (2.07 ± 0.09 mmol/L); and the PAE group, 8.56 ± 0.53 mg/dL (2.14 ± 0.13 mmol/L).

A summary of the time to reach the lowest calcium levels can be found in **Figure 4**. Calcium levels stabilized first in the TL group (15.54 ± 7.5 hours), significantly sooner than in all other groups ($P < .05$). Calcium levels stabilized in the PAE group at 23.76 ± 12.84 hours, followed by the TT group (25.07 ± 12.20 hours) and the SP group (31.00 ± 13.14 hours).

Preoperative 1,25-dihydroxyvitamin D levels were plotted against the lowest postoperative calcium levels for each group. The results for all patients combined are shown in **Figure 5**. No relationship was noted between preoperative 1,25-dihydroxyvitamin D levels and the lowest postoperative calcium levels when all patients were combined. Likewise, no relationship was noted between preoperative 1,25-dihydroxyvitamin D levels and the lowest postoperative calcium levels when patients were separated by treatment group.

Preoperative 1,25-dihydroxyvitamin D levels plotted against the time to reach the calcium nadir are shown in **Figure 6**. No relationship was noted between preoperative 1,25-dihydroxyvitamin D levels and the time to reach the lowest postoperative calcium levels when all patients were combined or when patients were separated by treatment group.

COMMENT

Recently, there has been a great deal of interest in identifying perioperative factors that can predict the devel-

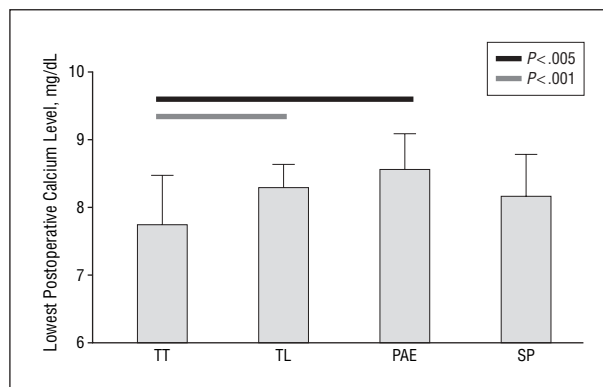


Figure 3. Lowest postoperative calcium levels separated by group. The total thyroidectomy (TT) group demonstrated the lowest average postoperative calcium level. Significant differences between groups are noted by the bars at the top of the graph. The error bars refer to the SD of the mean for each group represented. To convert calcium values to millimoles per liter, multiply by 0.25. TL indicates thyroid lobectomy; PAE, parathyroid adenoma excision; and SP, subtotal parathyroidectomy for hyperplasia.

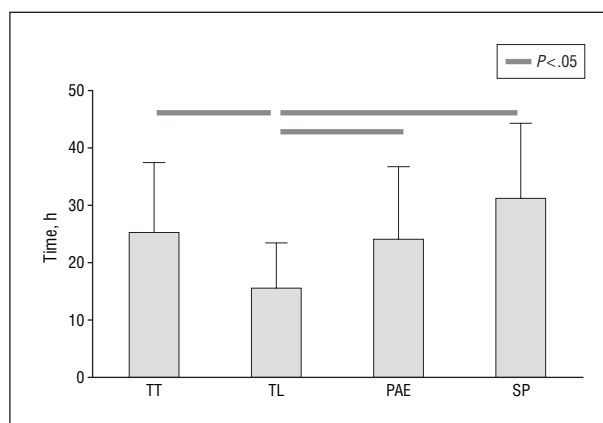


Figure 4. Time to reach the lowest postoperative calcium levels separated by treatment group. The calcium levels in the thyroid lobectomy (TL) group stabilized significantly faster than in all other treatment groups ($P < .05$ vs all other groups). The error bars refer to the SD of the mean for each group represented. TT indicates total thyroidectomy; PAE, parathyroid adenoma excision; and SP, subtotal parathyroidectomy for hyperplasia.

opment of hypocalcemia after thyroidectomy and parathyroidectomy. Those patients who can be identified as being at low risk for developing postoperative hypocalcemia can conceivably be treated on an outpatient or short-stay basis, which would result in considerable health care cost savings. Various investigators have looked at postoperative PTH levels²⁻⁵ as a predictor of the development of postoperative hypocalcemia after total or completion thyroidectomy. Lombardi et al² found that 15 of 16 patients who developed postthyroidectomy hypocalcemia had 4- and 6-hour postoperative PTH levels of less than 10 pg/mL (1.1 pmol/L). In a prospective study of 40 patients, Lam and Kerr⁴ noted that all 12 patients who developed postoperative hypocalcemia had 1-hour postoperative PTH levels that were less than or equal to 8 pg/mL (0.8 pmol/L). Pattou et al³ reported that a postoperative PTH level of 12 pg/mL (1.3 pmol/L) or less was very predictive of hypocalcemia. However, they did not report how many hours after surgery the PTH values were obtained.

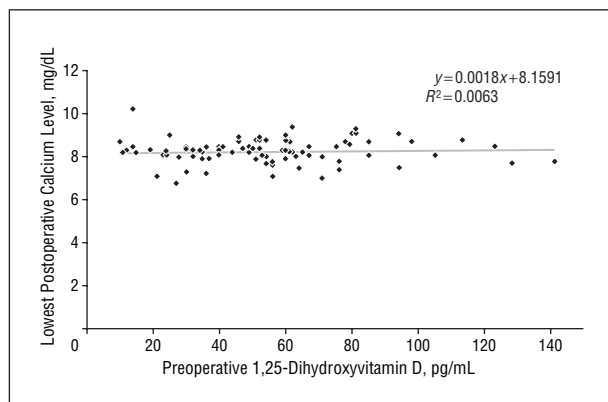


Figure 5. Preoperative 1,25-dihydroxyvitamin D levels plotted against lowest postoperative calcium levels. All patients within all 4 groups are included. No correlation was noted between preoperative 1,25 dihydroxyvitamin D levels and lowest postoperative calcium levels overall or when separated by group. To convert calcium values to millimoles per liter, multiply by 0.25.

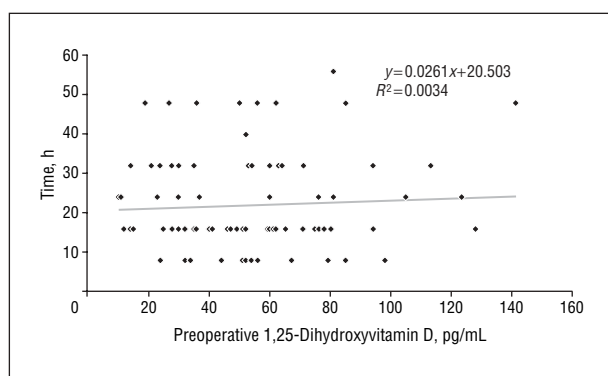


Figure 6. Preoperative 1,25-dihydroxyvitamin D levels plotted against time to reach lowest postoperative calcium levels. All patients within all 4 groups are included. No correlation was noted between preoperative 1,25 dihydroxyvitamin D levels and time to reach postoperative calcium nadir overall or when separated by group. To convert calcium values to millimoles per liter, multiply by 0.25.

In our series, all patients who developed hypocalcemia after total thyroidectomy had an 8-hour postoperative PTH level of less than 15 pg/mL (1.6 pmol/L) (sensitivity, 100%; specificity, 90.5%). These results are consistent with those of other authors²⁻⁴ and suggest that patients with 8-hour postoperative PTH levels of less than 15 pg/mL (1.6 pmol/L) after total thyroidectomy should undergo inpatient postoperative monitoring for the development of hypocalcemia. An alternative to consider would be the routine administration of calcium and calcitriol in such patients to facilitate stabilization of postoperative calcium levels, which could potentially shorten their hospital stay and reduce the risk of tetany. Patients undergoing total thyroidectomy with 8-hour postoperative PTH levels greater than 15 pg/mL (1.6 pmol/L) are at extremely low risk for developing postoperative hypocalcemia and can be considered for early discharge from the hospital if they are otherwise stable.

In our study, the patients in the TT group took significantly longer than those in the TL and PAE groups to achieve stable postoperative calcium levels. This tendency could be explained by the fact that during TT, there is potential for vascular compromise of all 4 parathy-

roid glands as a result of bilateral surgical manipulation. Intraoperative parathyroid trauma or ischemia may delay the recovery of parathyroid function after surgery. In contrast, patients in the TL and PAE groups had undisturbed parathyroid glands on the side that was not surgically treated.

Several investigators have also looked at intraoperative PTH levels as possible predictors of the development of postoperative hypocalcemia, with varying degrees of success.⁶⁻¹¹ However, a recent study determined that PTH levels continue to decrease for as long as 4 hours after TT.² This finding suggests that intraoperative PTH levels may have somewhat limited ability to predict postoperative hypocalcemia reliably after total or completion thyroidectomy.

As expected, no patients in the TL group in our study developed postoperative hypocalcemia. These patients presumably have undisturbed, normally functioning parathyroid glands on the side that was not operated on and have an extremely low risk of developing postoperative hypocalcemia. It has been suggested by some authors that thyroid lobectomies can be routinely performed on an outpatient basis.^{1,12}

Few studies have attempted to identify predictors of postoperative hypocalcemia after parathyroidectomy.^{6,13-16} In our study, no patients in the PAE group developed postoperative hypocalcemia, including those with 8-hour postoperative PTH levels of less than 15 pg/mL (1.6 pmol/L). It is our practice to perform unilateral exploration based on preoperative imaging studies to localize the adenoma, unless no obvious adenoma is identified on the first side explored. As a result, the contralateral parathyroid glands remain undisturbed, without risk of compromising their blood supply. A recent prospective, randomized study comparing unilateral with bilateral neck exploration for primary hyperparathyroidism¹⁷ found an increased incidence of hypocalcemia and significantly lower postoperative calcium levels in patients undergoing bilateral exploration. Only 5 of 34 patients with primary hyperparathyroidism in our study underwent bilateral exploration, likely contributing to the low rate of hypocalcemia in our patients.

Another factor in our study that might have contributed to the absence of postoperative hypocalcemia after PAE is that we used a lower cutoff postoperative calcium level (7.0 mg/dL [1.8 mmol/L]) for calcium replacement than other authors. The normal parathyroid glands in patients with primary hyperparathyroidism are suppressed by the hyperfunctional adenoma. There is a period of recovery after the adenoma is removed before these suppressed glands function normally. A delayed recovery of suppressed glands in primary hyperparathyroidism is supported by our findings that postoperative calcium levels took significantly longer to stabilize in patients who underwent PAE than in patients who underwent TL even though the patients in the PAE group had undisturbed parathyroid glands on the side that was not surgically treated. Therefore, allowing the serum calcium levels to reach lower levels than the limits set by other authors may stimulate the suppressed glands to begin functioning.

Our results suggest that patients with single parathyroid adenomas who undergo unilateral exploration are

at very low risk for developing postoperative hypocalcemia and may be candidates for outpatient or short-stay surgery. Patients who are at high risk for hungry bone syndrome, such as elderly patients or those who have very large adenomas, however, should be more closely monitored. Further studies with larger patient numbers would be required to confirm our findings.

In our study, we found that patients in the SP group who had 8-hour postoperative PTH levels of less than 15 pg/mL (1.6 pmol/L) were at high risk for developing hypocalcemia, with 75% of them requiring calcium replacement. When performing these surgical procedures, we attempt to preserve the vascular supply to the parathyroid remnant when possible. A low postoperative PTH level may indicate that this blood supply is inadequate and that early postoperative calcium and calcitriol supplementation is indicated.

No patient in our study developed a postoperative hematoma. Hematoma, which is a potentially devastating complication after thyroid and parathyroid surgery, usually occurs within 24 hours of surgery. Fortunately, neck hematomas only occur in approximately 1.2% to 1.6% of patients.^{3,18} However, given the potentially fatal consequences, surgeons must consider their level of comfort before performing these procedures on an outpatient basis. Since hematomas usually occur within 24 hours of surgery, overnight observation with early discharge may be more prudent than outpatient surgery, even in those patients who are at low risk for developing postoperative hypocalcemia.

Vitamin D plays a critical role in calcium metabolism. It is stored in fat cells and is converted to 25-hydroxyvitamin D in the liver, followed by conversion to 1,25-dihydroxyvitamin D in the kidney. This activated form of vitamin D then increases calcium absorption in the intestine. We hypothesized that those patients with higher serum levels of vitamin D (and indirectly in fatty tissue) may be able to mobilize these reserves in conditions of an acute decrease in PTH levels or hypocalcemia. However, this hypothesis was not supported by our data, as there was no correlation between preoperative levels of 1,25-dihydroxyvitamin D and postoperative calcium levels.

CONCLUSIONS

Patients who undergo TL and single PAE with unilateral neck exploration are at extremely low risk for developing postoperative hypocalcemia. Patients who undergo TT or SP and have 8-hour postoperative PTH levels of 15 pg/mL (1.6 pmol/L) or higher are at low risk for developing postoperative hypocalcemia. These subgroups of patients can be considered for early discharge from the hospital.

Patients who undergo TT or SP and have 8-hour postoperative PTH levels of less than 15 pg/mL (1.6 pmol/L) are at very high risk for developing postoperative hypocalcemia. These patients should have their serum calcium levels monitored closely and should be considered

for early administration of oral calcium and vitamin D supplementation. Preoperative levels of 1,25-dihydroxyvitamin D did not correlate with postoperative calcium levels and were not a useful predictor of postoperative hypocalcemia.

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Correspondence: Lisa A. Orloff, MD, Department of Clinical Otolaryngology–Head and Neck Surgery, University of California, San Francisco, 2380 Sutter St, Second Floor, San Francisco, CA 94115 (LOrloff@ohns.ucsf.edu).

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REFERENCES

- McHenry CR. "Same-day" thyroid surgery: an analysis of safety, cost savings, and outcome. *Am Surg*. 1997;63:586-589.
- Lombardi CP, Raffaelli M, Princi P, et al. Early prediction of postthyroidectomy hypocalcemia by one single iPTH measurement. *Surgery*. 2004;136:1236-1241.
- Pattou F, Combemale F, Fabre S, et al. Hypocalcemia following thyroid surgery: incidence and prediction of outcome. *World J Surg*. 1998;22:718-724.
- Lam A, Kerr PD. Parathyroid hormone: an early predictor of postthyroidectomy hypocalcemia. *Laryngoscope*. 2003;113:2196-2200.
- Payne RJ, Hier MP, Tamilia M, Mac Namara E, Young J, Black MJ. Same-day discharge after total thyroidectomy: the value of 6-hour serum parathyroid hormone and calcium levels. *Head Neck*. 2005;27:1-7.
- Warren FM, Andersen PE, Wax MK, Cohen JL. Intraoperative parathyroid hormone levels in thyroid and parathyroid surgery. *Laryngoscope*. 2002;112:1866-1870.
- Richards ML, Bingener-Casey J, Pierce D, Strodel WE, Sirinek KR. Intraoperative parathyroid hormone assay: an accurate predictor of symptomatic hypocalcemia following thyroidectomy. *Arch Surg*. 2003;138:632-636.
- Warren FM, Andersen PE, Wax MK, Cohen JL. Perioperative parathyroid hormone levels in thyroid surgery: preliminary report. *Laryngoscope*. 2004;114:689-693.
- Lindblom P, Westerdahl J, Bergenfelz A. Low parathyroid hormone levels after thyroid surgery: a feasible predictor of hypocalcemia. *Surgery*. 2002;131:515-520.
- Lo CY, Luk JM, Tam SC. Applicability of intraoperative parathyroid hormone assay during thyroidectomy. *Ann Surg*. 2002;236:564-569.
- Higgins KM, Mandell DL, Govindaraj S, et al. The role of intraoperative rapid parathyroid hormone monitoring for predicting thyroidectomy-related hypocalcemia. *Arch Otolaryngol Head Neck Surg*. 2004;130:63-67.
- de Pasquale L, Schubert L, Bastagli A. Post-thyroidectomy hypocalcemia and feasibility of short-stay thyroid surgery. *Chir Ital*. 2000;52:549-554.
- Gurnell EM, Thomas SK, McFarlane I, et al. Focused parathyroid surgery with intraoperative parathyroid hormone measurement as a day-case procedure. *Br J Surg*. 2004;91:78-82.
- Wong WK, Wong CS, Farndon JR. Early postoperative plasma calcium concentration as a predictor of the need for calcium supplement after parathyroidectomy. *Br J Surg*. 1996;83:532-534.
- 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.
- Mittendorf EA, Merlino JL, McHenry CR. Post-parathyroidectomy hypocalcemia: incidence, risk factors, and management. *Am Surg*. 2004;70:114-120.
- Bergenfelz A, Lindblom P, Tibblin S, Westerdahl J. Unilateral versus bilateral neck exploration for primary hyperparathyroidism: a prospective randomized controlled trial. *Ann Surg*. 2002;236:543-551.
- Reeve T, Thompson NW. Complications of thyroid surgery: how to avoid them, how to manage them and observations on their possible effect on the whole patient. *World J Surg*. 2000;24:971-975.