Intraoperative Parathormone Measurements and Postoperative Hypocalcemia

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ABSTRACT: **Background:** Hypocalcemia following thyroid and parathyroid surgery is a well-recognized potential complication.

Objectives: To determine the utility of intraoperative quick parathormone assay in predicting severe hypocalcemia development following parathyroidectomy for a single-gland adenoma causing primary hyperparathyroidism.

Methods: A retrospective cohort study was performed. IO-QPTH values were measured at time 0 (T_0) before incision, and 10 (T_{10}) and 30 minutes (T_{30}) following excision of the hyperfunctioning gland. Percent decrease in IO-QPTH at 10 minutes (T_{10}), maximum percent decrease of IO-QPTH value, and lowest actual IO-QPTH value obtained at surgery were used to determine any correlation with the development of postoperative hypocalcemia requiring treatment.

Results: Percent decrease in IO-QPTH at 10 minutes, maximum percent decrease in IO-QPTH and lowest IO-QPTH value did not correlate with the lowest postoperative calcium levels measured 18 hours after surgery ($r = 0.017$, $P = 0.860$; $r = 0.018$, $P = 0.850$; and $r = 0.002$, $P = 0.985$ respectively). For the purposes of our analysis, patients were subdivided into three groups. Group 1 comprised 68 patients with normal calcium levels (serum Ca 8.6–10.3 mg/dl), group 2 had 28 patients with hypocalcemia (8.1–8.6 mg/dl), and group 3 included 12 patients with severe hypocalcemia (calcium level ≤ 8.0 mg/dl) requiring calcium supplementation due to symptoms of hypocalcemia. There was no difference between the three groups in the lowest IO-QPTH value ($P = 0.378$), percent decrease in IO-QPTH ($P = 0.305$) and maximum percent decrease in IO-QPTH ($P = 0.142$).

Conclusions: IO-QPTH evaluation was not useful in predicting the group of patients susceptible to develop severe postoperative hypocalcemia.

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KEY WORDS: parathyroidectomy, hypocalcemia, quick PTH, hyperparathyroidism, parathormone

IO-QPTH = intraoperative quick parathormone

Hypocalcemia following thyroid and parathyroid surgery is a well-recognized potential complication and is one of the factors determining the length of hospital postoperative stay [1-3]. The cited rates of hypocalcemia following parathyroidectomy vary from as low as 10% to as high as 46%, depending on the technique used – bilateral or unilateral neck exploration [4-7]. The etiology of postoperative hypocalcemia has not been definitively elucidated. However, several mechanisms have been proposed, including parathyroid insufficiency related to injury or devascularization of the parathyroid glands, the calciuretic effect of intraoperative fluid administration, decreased parathormone secretion from atrophic glands, and hungry bone syndrome related to remineralization of the skeleton [6,7].

To improve the success rate of parathyroidectomy, intraoperative quick parathormone assay is being used to confirm successful extirpation of the hyperfunctioning parathyroid tissue. The accepted definition of successful parathyroidectomy is a 50–70% decrease in IO-QPTH levels measured 10 minutes following excision of the hyperfunctioning parathyroid tissue [8-14].

Although many studies have dealt with the use of IO-QPTH monitoring as a measure for determining the likelihood of surgical cure, only a few publications have dealt with the question of whether or not the percent decrease at 10 minutes following excision of the hyperfunctioning gland may also serve as useful predictive information regarding the development of severe, early postoperative hypocalcemia [3-5,15]. The purpose of the present study was to determine the utility of the IO-QPTH assay in predicting early, symptomatic, postoperative hypocalcemia requiring calcium supplementation in patients undergoing a single adenoma excision for primary hyperparathyroidism.

PATIENTS AND METHODS

This was a retrospective study based on 108 patients. The investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the local Ethics Committee. Patient consent was waived.

The study group comprised 108 patients with primary hyperparathyroidism. The diagnosis of PHPT was based on high plasma calcium and PTH levels, low plasma phosphor levels, and quantitative high 24 hour urine calcium and phosphor levels. All patients underwent preoperative localization by MIBI scan and ultrasound of the neck. In all patients, excision of a single parathyroid adenoma was performed using the minimally invasive technique.

QUICK PTH MEASUREMENT

Quick parathormone assays were performed during the operation using Immulite Turbo Intact PTH kit (DPC, Los Angeles, CA, USA). IO-QPTH levels were measured at time zero (T^0) (before the incision) and at 10 (T^{10}) and 30 (T^{30}) minutes following excision of the suspected hyperfunctioning parathyroid gland. Blood samples were drawn into EDTA tubes and sent on ice via a pneumatic tubing system to the laboratory, centrifuged for 5 minutes and immediately evaluated. Only a drop of 60% or more in IO-QPTH levels from zero time was considered a positive result.

PATHOLOGY

All excised specimens were sent for frozen section evaluation. The decision to end the surgical procedure was based on the accumulation of laboratory data and the pathological report.

ISOTOPE STUDIES

A gamma detector was used in all patients. One hour prior to surgery, patients were injected with Tc99m MIBI at the Institute of Nuclear Medicine, and the possible location of the hyperfunctioning gland was marked on the skin of the neck in those patients in whom it could be located.

CALCIUM MEASUREMENT

Serum calcium levels were measured 18 hours postoperatively. Hypocalcemia was considered when the calcium level was below 8.6 mg/dl (normal range 8.6–10.3 mg/dl). Severe hypocalcemia was considered when the calcium level dropped to any level below 8.0 mg/dl with symptoms of hypocalcemia requiring calcium supplementation. Patients were treated for signs or symptoms of hypocalcemia by intravenous and oral calcium supplements, with oral 1-alpha-OH D3, and remained hospitalized until their calcium levels stabilized. If calcium measurements 18 hours postoperatively were ≥ 8.1 mg/dl the patients were discharged, while patients with calcium levels ≤ 8.0 mg/dl remained in hospital for further follow-up.

STATISTICAL ANALYSIS

The percent decrease at 10 minutes (T^{10}), maximum percent decrease of IO-QPTH and lowest actual IO-QPTH value obtained at surgery were used to determine any correlation with the development of postoperative hypocalcemia requiring treatment. The percent decrease in IO-QPTH at 10 minutes was calculated using the baseline at zero time (before incision) of IO-QPTH and the value of IO-QPTH 10 minutes following excision of the single hyperfunctioning parathyroid gland. The maximum percent decrease in IO-QPTH value was calculated using the baseline IO-QPTH value and the lowest IO-QPTH value measured after excision of the hyperfunctioning parathyroid gland (the lowest IO-QPTH value achieved at T^{10} or T^{30} following excision of the hyperfunctioning parathyroid gland).

Statistical analysis was performed at the Tel Aviv University Department of Statistics using the non-parametric Mann-Whitney U test, one-way ANOVA test, the Spearman rank correlation method and Student's *t*-test.

PHPT = primary hyperparathyroidism
PTH = parathormone

RESULTS

We evaluated 108 patients with PHPT who underwent parathyroidectomy for a single adenoma and IO-QPTH monitoring. The patients, 72 females and 36 males, ranged in age from 23 to 85 years. The mean IO-QPTH level at time zero was 35.09 ± 25.15 pmol/L, ranging from 8.5 to 145 pmol/L (normal 0.99–5.94). At 10 minutes post-excision of the hyperfunctioning gland, IO-QPTH levels dropped by a mean of 82.3%, from 35.09 pmol/L to 5.60 ± 18.78 pmol/L. Forty of the 108 evaluated patients (37%) experienced postoperative hypocalcemia (serum Ca ≤ 8.6 mg/dl) and 12 of these 40 experienced severe hypocalcemia (calcium level ≤ 8.0 mg/dl requiring calcium supplementation due to symptoms of hypocalcemia).

The percent decrease in IO-QPTH value, the maximum percent decrease in IO-QPTH and the lowest IO-QPTH value did not correlate with the lowest postoperative calcium value measured 18 hours postoperatively ($r = 0.017$, $P = 0.860$; $r = 0.018$, $P = 0.850$; and $r = 0.002$, $P = 0.985$ respectively). No statistically significant difference was found between the group with normal calcium levels (68 patients) and the group with hypocalcemia (40 patients) in the lowest IO-QPTH value ($P = 0.468$), percent decrease in IO-QPTH ($P = 0.898$), and maximum percent decrease in IO-QPTH value ($P = 0.855$). The mean lowest IO-QPTH value in the group with normal calcium levels was 2.71 ± 1.76 pmol/L with a mean percent decrease of 83.4%. In the group of patients with postoperative hypocalcemia, the mean lowest IO-QPTH value was 2.68 ± 2.37 pmol/L and the mean percent decrease was 79.2%.

For the purposes of our analysis, the patients were subdivided into three groups. Group 1 comprised 68 patients with normal calcium levels (serum Ca 8.6–10.3 mg/dl); Group 2 had 28 patients with hypocalcemia (serum Ca 8.1–8.6 mg/dl); and Group 3 consisted of 12 patients with severe hypocalcemia (calcium level ≤ 8.0 mg/dl) requiring

Table 1. Correlation of intraoperative quick parathormone values with postoperative hypocalcemia

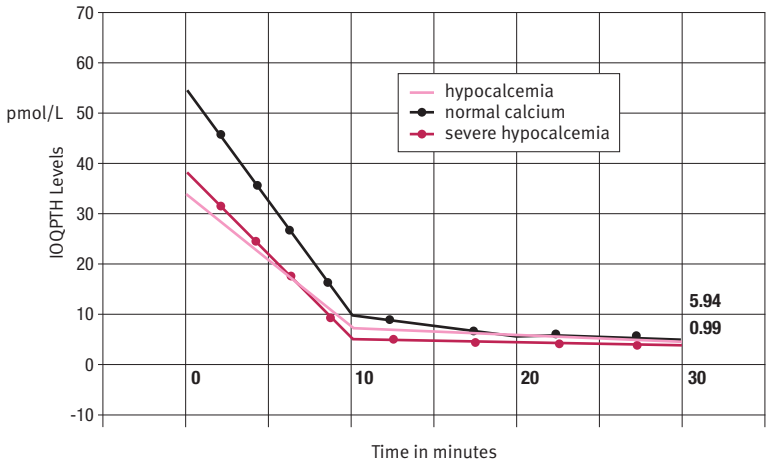
	Postoperative normocalcemia (8.6–10.3 mg/dl)	Postoperative hypocalcemia (8.1–8.6 mg/dl)	Severe postoperative hypocalcemia (< 8.1 mg/dl)
Percent decrease in IO-QPTH*	83.4%	81.9%	71.52%
Maximum percent decrease in IO-QPTH**	88.3%	89.4%	90.45%
Lowest IO-QPTH value	2.71 ± 1.76 pmol/L	2.68± 2.44 pmol/L	2.67 ± 1.88 pmol/L

*Percent decrease in IO-QPTH is the percent decrease in IO-QPTH values from the value at T0 (before incision) to the value at time T10 (10 minutes following excision).

**Maximum percent decrease in IO-QPTH is the percent decrease in IO-QPTH values from the value at T0 to the lowest value of IO-QPTH achieved.

IO-QPTH = intraoperative quick parathormone

Figure 1. Graphic presentation of the intraoperative quick parathormone levels



calcium supplementation due to symptoms of hypocalcemia. There was no difference between the three groups in the lowest IO-QPTH (P = 0.378), percent decrease in IO-QPTH (P = 0.305) and maximum percent decrease in IO-QPTH (P = 0.142). The mean lowest IO-QPTH value in the group with normal calcium levels was 2.71 ± 1.76 pmol/L, the percent decrease in IO-QPTH was 83.4%, and the maximum percent decrease in IO-QPTH was 88.3%. In the group of patients with postoperative hypocalcemia, the mean lowest IO-QPTH value was 2.68 ± 2.44 pmol/L, the percent decrease in IO-QPTH was 81.9% and the maximum percent decrease in IO-QPTH 89.4%. The mean lowest IO-QPTH value in the group of patients with severe hypocalcemia was 2.67 ± 1.88 pmol/L, the percent decrease in IO-QPTH was 71.52% and the maximum percent decrease in IO-QPTH was 90.45% [Table 1, Figure 1].

DISCUSSION

Vocal cord paralysis, hemorrhage and hypocalcemia are the most common complications of thyroid and parathyroid surgery [1-3,15,16]. While vocal cord paralysis and postoperative hemorrhage generally occur in the immediate postoperative course, hypocalcemia is usually observed somewhat later [8,17,18]. Routinely, serum calcium levels are measured at several points postoperatively to ensure normocalcemia before discharge [1,2,8-11,16]. As severe postoperative hypocalcemia may require prolonged postoperative hospitalization, prediction of postoperative hypocalcemia could define the group of patients requiring hospitalization versus those who can be discharged on the day of surgery [1-3,15,16].

Based on our experience with IO-QPTH measurements in patients with primary hyperparathyroidism, we explored the question whether IO-QPTH monitoring would be helpful in predicting this highly specific group of patients with a high risk of postoperative hypocalcemia. Three points were studied: a) the percent decrease of IO-QPTH – from time zero (T^0) to 10 minutes (T^{10}), b) the maximum percent decrease of IO-QPTH, and c) the lowest actual IO-QPTH obtained at surgery. Although small differences were noticed between the study groups, these differences were not statistically significant and could not be used to define any specific algorithm of a patient likely to develop severe postoperative hypocalcemia.

Various studies have shown that IO-QPTH monitoring can be used for predicting surgical cure in patients undergoing surgery for PHPT [4,8-12]. However, a literature search revealed scarce data regarding the value of this assay in predicting postoperative hypocalcemia in patients undergoing surgery for primary hyperparathyroidism [4,12,13]. On the other hand, we found many studies of hypocalcemia following thyroidectomy [2,3,16,19-21].

There is considerable controversy in the literature regarding the utility of IO-QPTH measurement for prediction of postoperative hypocalcemia in patients undergoing surgery for primary hyperparathyroidism. Warren et al. [16] studied 30 patients undergoing IO-QPTH monitoring during parathyroid exploration and 23 patients during thyroid surgery. The authors concluded that intraoperative PTH levels > 15 pg/ml after total thyroidectomy indicate a low risk of postoperative hypocalcemia, but that intraoperative PTH levels (as in our study) do not correlate with postoperative calcium levels in the parathyroid group. In the study of Elaraj and co-researchers [15], IO-QPTH monitoring was able to predict postoperative hypocalcemia, but this correlation was significant only in multiglandular disease and not in patients with a single adenoma as in our study. The maximum percent decrease in IO-QPTH in their study was ≥ 84%. In contrast to

our study, Shoman et al. [4] did find a correlation between the percentage change in IO-QPTH and the development of postoperative hypocalcemia following parathyroidectomy. The authors concluded that the percentage change in IO-QPTH may represent an accurate and important predictive tool.

Some studies on the importance of IO-QPTH in predicting postoperative hypocalcemia for patients undergoing thyroidectomy demonstrated a correlation between IO-QPTH values and postoperative hypocalcemia. Lo et al. [2] conducted a study on the applicability of intraoperative hormone assay during thyroidectomy. No patient undergoing parathyroid surgery was included in this study. The authors concluded that IO-QPTH monitoring during thyroidectomy enables the identification of patients at risk to develop postoperative hypocalcemia. In the study by Quiros and colleagues [3], 72 patients undergoing thyroid surgery underwent IO-QPTH monitoring, and the authors concluded that an IO-QPTH level < 10 pg/ml is a strong predictor of hypoparathyroidism after thyroid surgery. The study by Richards and team [19], although in a relatively small group of patients, showed a correlation between an IO-QPTH level < 10 pg/ml and postoperative hypocalcemia. In addition, Higgins et al. [20] concluded from their findings that intraoperative PTH monitoring is useful in predicting postoperative hypocalcemia following total thyroidectomy. Friedman and collaborators [21] indicated the usefulness of intraoperative PTH monitoring in the process of decision making when considering reimplanting a parathyroid gland following thyroidectomy. The literature data suggest that IO-QPTH values may correlate with postoperative hypocalcemia only in cases of multiglandular disease or thyroidectomy with excision of more than one parathyroid gland, and not in cases of a single adenoma.

In conclusion, in our study of IO-QPTH monitoring for primary hyperparathyroidism caused by a single adenoma in 108 patients, we were unable to define or predict those patients who would develop severe postoperative hypocalcemia requiring treatment.

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"Once you label me you negate me"

Soren Kierkegaard (1813-1855), Danish philosopher. Much of his philosophical work deals with the issues of how one lives, focusing on the priority of concrete human reality over abstract thinking and highlighting the importance of personal choice and commitment. His theological work focuses on Christian ethics and the institution of the Church; his psychological works explore the emotions of individuals when faced with life choices