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Predictors of operative failure in parathyroidectomy for primary hyperparathyroidism

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ABSTRACT

Introduction: Many adjuncts guide surgical decision making in parathyroidectomy, yet their independent associations with outcome are poorly characterized. We examined a broad range of perioperative factors and used multivariate techniques to identify independent predictors of operative failure (persistent disease) after parathyroidectomy.
Methods: This was a retrospective review of 2239 patients with primary hyperparathyroidism who underwent parathyroidectomy at a single-center from 1999 to 2014. We used multivariate logistic regress to measure associations between multiple perioperative factors and an operative failure (persistent hypercalcemia).
Results: Operative failure was identified in 67 patients (3.0%). The following variables were independently associated with operative failure on multivariate analysis: IOPTH criteria met (protective, $OR = 0.22$, $P < 0.001$), preoperative calcium (risk factor, $OR = 2.27$ per unit increase, $P < 0.001$), weight of excised gland(s) (protective, $OR = 0.70$ per two-fold increase, $P = 0.003$), and preoperative PTH (protective, $OR = 0.55$ per two-fold increase, $P = 0.008$).
Conclusion: In addition to the well-established IOPTH criteria, we suggest that consideration of the above independent perioperative risk factors may further inform surgical decision-making in parathyroidectomy.

1. Introduction

Primary hyperparathyroidism (PHPT) has an incidence of 1–2% in the adult population, and parathyroidectomy is the only cure.[1] Surgical decision-making in parathyroidectomy is guided largely by preoperative imaging and intraoperative parathyroid hormone (IOPTH) monitoring. Preoperative imaging can include sestamibi ± single-photon emission computed tomography (SPECT), cervical ultrasound, and 4D-computed tomography scan.[2,3] IOPTH monitoring is frequently used to ensure appropriate resection and biochemical cure.[4] In experienced centers, success rates for parathyroidectomy for PHPT range from 92% to 99%.[3,5–11] Nevertheless, failure does occur after this common surgery, yet failure is infrequently studied.

Little is known about patient-level predictors of operative failure and persistent PHPT. Previous studies have attributed operative failure to inadequate preoperative imaging localization.[3,5,10] Achievement of IOPTH criteria is a known predictor of operative success, though the final target IOPTH level is not agreed upon. Some researchers contend that final IOPTH levels should fall into the normal range,[4,9] while others recommend lower levels.[6] The independent contributions of preoperative localization, IOPTH biochemical cure, and preoperative biochemical severity to operative success are unclear. Better understanding of the relationship

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of these factors to operative failure is necessary to further improve outcomes after this surgery and optimize intraoperative decision-making.

We investigated predictors of operative failure (persistent disease) in patients undergoing parathyroidectomy for PHPT. Using multivariate logistic regression, we evaluated the independent effects of the following factors: demographics, preoperative biochemical disease severity, preoperative imaging, IOPTH criteria, and histopathologic findings. We aimed to identify a subset of independent risk factors for operative failure.

2. Methods

2.1. Study population

This was a retrospective analysis of a prospectively maintained, Institutional Review Board approved database containing patients who underwent parathyroidectomy for PHPT at the University of Michigan Health System between 1999 and 2014. We excluded patients with the following: secondary or tertiary hyperparathyroidism, reoperative parathyroidectomy, multiple endocrine neoplasia type 1, and history of lithium use.

2.2. Preoperative factors

Preoperative laboratory measurements included peak serum calcium and serum PTH levels (biochemical severity of disease). Nearly all study patients underwent preoperative imaging for gland localization, including surgeon performed ultrasound and/or sestamibi scan ± SPECT. At our institution, ultrasound is the primary imaging modality and is performed by the endocrine surgeon during initial clinical evaluation. Sestamibi is ordered if ultrasound is non-localizing or equivocal. For logistic regression analysis, the imaging localization variable was coded as: neither imaging modalities localizing or no imaging performed (the reference group), ultrasound or sestamibi localizing, ultrasound and sestamibi localizing but discordant, or ultrasound and sestamibi localizing and concordant. Imaging was considered correct if the diseased glands were located intraoperatively on the same side as indicated by imaging (without distinguishing superior/inferior). If imaging suggested an adenoma but multiglandular disease was discovered intraoperatively, this was considered incorrect imaging. The imaging correctness variable was coded as: neither imaging modalities correct or no imaging performed (the reference group), ultrasound or sestamibi correct, or both ultrasound and sestamibi correct.

Patients with positive localizing studies were candidates for minimally invasive parathyroidectomy (MIP). A bilateral exploration was elected in absence of localization or for high preoperative suspicion of multiglandular disease. For logistic regression analysis, the variable of interest was four-gland operation (either planned or converted). IOPTH monitoring was used in nearly every case. Levels were drawn from the jugular vein or peripherally at initiation of surgery and/or just prior to parathyroid gland excision and at 5, 10, and 15 min post-excision. Baseline IOPTH was defined as the highest value of two samples recorded following anesthesia induction and immediately prior to gland excision. Biochemical cure was defined as both a decrease in IOPTH ≥50% from baseline and a post-excision IOPTH within the normal range (12–75 pg/mL). MIP was converted to four-gland exploration intraoperatively if IOPTH criteria was not achieved, localization was incorrect, or multiglandular disease was otherwise suspected. The variable of interest in analysis was achievement of IOPTH criteria (biochemical cure). In rare cases, IOPTH criteria was not achieved prior to completion of an operation. For example, IOPTH monitoring was sometimes ceased upon conversion to four-gland operation in lieu of morphologic analysis of enlarged hyperplastic parathyroid glands. Additionally, patients with low baseline PTH (<100 pg/mL) may have final IOPTH levels that fall into normal range yet do not meet criteria of decreasing ≥50% from baseline.

The number of parathyroid glands excised was dichotomized to *single gland or multiple glands* for the analysis. We did not distinguish between hyperplasia and adenoma based on pathological analysis, as this is generally considered a difficult distinction. Total weight of the excised gland(s) was recorded from the pathology report.

2.3. Outcome

Postoperative serum calcium values were collected on all patients. The lowest and highest postoperative calcium levels were recorded. At the time of analysis, for patients with peak postoperative serum calcium levels ≥10.2 mg/dL, charts were retrospectively reviewed for additional follow-up to rule out transient postoperative hypercalcemia, and to verify outcome. The outcome of interest was operative failure with resultant persistent hyperparathyroidism. Persistent disease was defined by postoperative serum calcium measurements persistently ≥10.2 mg/dL or a single calcium ≥11.0 mg/dL when no additional data was available (all measurements within 6 months postoperatively). Postoperative PTH labs are not routinely ordered at our institution, and thus PTH was not a component of the definition of failure. Due to biochemical followup constraints, recurrent disease (incidence beyond 6 months postoperatively) was not assessed or analyzed.

2.4. Statistical analysis

Pairwise comparisons were computed using a Student's t-test, Wilcoxon rank-sum test, or Fisher's exact test, as appropriate. The following variables were considered as potential predictors of operative failure: age, sex, preoperative peak PTH, preoperative peak calcium, imaging localization, imaging correctness, four-gland approach, achievement of IOPTH criteria, number of glands excised, and total weight of excised gland(s). Highly skewed variables were transformed using a logarithm of base two. Univariate and multivariate logistic regression were utilized to assess the associations between the perioperative factors and operative failure. For multivariate analysis, we randomly divided our sample into a training set (60% of sample) and an internal validation set (40% hold-out sample) to assess predictive ability of the models. Backward stepwise selection was used to identify independent predictors of operative failure ($P \leq 0.100$ for inclusion in the model). Because our predictors of interest included both preoperative and intraoperative variables, we developed two main models: a preoperative model and a combined intraoperative model (the latter considered all variables). Hosmer-Lemeshow test was used to ensure model goodness of fit. Variance inflation factor was used to ensure no problems with multicollinearity. Area under the receiver operating characteristic curve (AUROC) was used to assess model predictive ability.

We performed secondary analyses to evaluate consistency of our findings. First, we grouped preoperative calcium and PTH by tertile, and we examined rates of operative failure by tertile of calcium and PTH. As a secondary outcome, we assessed predictors of elevated postoperative calcium (calcium ≥10.2 mg/dL regardless of persistence; binary outcome) using logistic regression. To determine if any statistical effects were mediated by the number of