

Long-term Results of Parathyroidectomy for Hypercalcemic Crisis

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Hypothesis: Hypercalcemic crisis is a rare complication of severe calcium intoxication usually caused by sporadic primary hyperparathyroidism that requires prompt diagnosis and definitive surgical treatment. Parathyroidectomy is essential for long-term successful treatment of hypercalcemic crisis.

Design: Retrospective case series.

Setting: Tertiary referral center.

Patients: Forty-three patients treated for hypercalcemic crisis during a 35-year period who had signs and symptoms of acute calcium intoxication and serum calcium levels of 15 mg/dL (3.75 mmol/L) or greater.

Main Outcome Measures: Operative success, operative failure, and disease recurrence after surgery. Kaplan-Meier analysis was used to estimate long-term survival after parathyroidectomy.

Results: Forty-two (98%) of 43 patients were eucalcemic after initial parathyroidectomy. There was 1 postoperative death. Of 27 patients with postoperative calcium data available for 6 months or longer, operative success was achieved in 26 (96%). There was 1 operative failure in a patient with multiglandular disease requiring reoperation. There were 3 recurrences (7%) at 7, 58, and 265 months. Overall median survival after parathyroidectomy was 11.7 years (95% confidence interval, 9.2-NE [not estimable]). The mean±SD serum calcium level of this group at a median follow-up of 4 years after surgery was 9.1±0.9 mg/dL (2.28±0.23 mmol/L).

Conclusion: Hypercalcemic crisis can be successfully treated by parathyroidectomy with continued normal parathyroid function and excellent long-term survival.

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HYPERCALCEMIC CRISIS IS A rare, life-threatening complication of severe calcium intoxication. The cause of this clinical syndrome is usually sporadic primary hyperparathyroidism or advanced malignancy.^{1,2} Earlier reports have attributed the high mortality of this disease to failure of a correct diagnosis or inappropriate clinical management.³⁻⁵ The acute severity of

condition has been described, long-term results including parathyroid gland function, recurrent disease, and survival after definitive parathyroidectomy remain unknown. This study describes the surgical outcome and long-term results of patients with hypercalcemic crisis after parathyroidectomy.

METHODS

A review of 1055 consecutive patients who underwent parathyroidectomy at this institution from January 1, 1969, through October 31, 2004, identified 43 patients treated for hypercalcemic crisis. This condition was defined in patients with signs and symptoms of acute calcium intoxication, including mental status changes, extreme fatigue, severe dehydration, and results of biochemical studies that confirmed the diagnosis. These patients had serum calcium levels of 15 mg/dL (3.75 mmol/L) or greater and elevated parathyroid hormone (PTH) levels. Although C-terminal parathyroid assays were first used in 1972, a 2-site antibody assay for measuring the intact PTH (1-84) molecule was used after 1990.

Some patients in this series were initially treated at outside hospitals for extreme hypercalcemia. On admission to this institution, all

See Invited Critique at end of article

hypercalcemic crisis is associated with elevated serum calcium levels greater than 15 mg/dL (3.75 mmol/L) and rapid deterioration of central nervous system, cardiac, gastrointestinal, and renal function.⁶⁻¹¹ Since the first description of this condition in 1932, numerous studies have reported that early diagnosis, emergent preoperative medical management, and expeditious parathyroidectomy provide the best course of treatment for hypercalcemic crisis.^{8-10,12-14} Although the immediate success in treating patients with this

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patients promptly received intravenous isotonic sodium chloride solution infusions and loop diuretics for rehydration and to lower their serum calcium levels. Hypocalcemic drugs such as bisphosphonates were also used as adjuncts for lowering serum calcium level. In earlier years, bilateral neck exploration with attempted visualization of all parathyroid glands and resection of enlarged glands based on surgeon's judgment and histopathologic findings was performed at this institution. When more than 1 enlarged gland was excised or if persistent postoperative hypercalcemia occurred after the excision of 1 enlarged gland, the patient was determined to have multiglandular disease (MGD). After 1993, the operative approach was converted to limited parathyroidectomy that involves preoperative parathyroid gland localization and excision guided by intraoperative PTH assay. Patients with more than 1 hypersecreting parathyroid gland measured by intraoperative PTH assay were determined to have MGD.

Calcium and cholecalciferol (vitamin D) supplements were often administered postoperatively when profound hypocalcemia was anticipated in this group of patients with longstanding disease and severe bone mineral loss. When possible, serum calcium levels were monitored immediately postoperatively, at 2 and 6 months, and then at yearly intervals. Operative success was defined as eucalcemia for 6 months or longer after parathyroidectomy. Operative failure was defined in patients with elevated serum calcium and PTH levels within 6 months after parathyroidectomy. Recurrence was defined as elevated serum calcium and PTH levels after 6 months of eucalcemia. Postoperative mortality was defined as patient death occurring less than 30 days after surgery.

Outcome measurements were operative success and failure, recurrence, and length of survival. Characteristics of patients at the time of surgery are presented as frequencies and mean \pm SD. The Kaplan-Meier product-limit method from the date of surgery was used to estimate survival distributions with the corresponding 95% confidence intervals. Univariate hazard ratios were calculated for each of the variables by means of Cox proportional hazards regression. Statistical analyses were performed with SAS version 9.1 software (SAS Institute Inc, Cary, NC). $P \leq .05$ was considered statistically significant.

RESULTS

The majority of the patients were women ($n=27$). The mean age of the entire group was 60 years (range, 21-79 years), and most patients presented with a medical history of hypertension, weight loss, hyperparathyroidism, renal insufficiency, and kidney stones (**Table 1**). The most common presenting symptoms in 38 patients included musculoskeletal complaints (eg, muscle weakness and bone pain), fatigue, mental status changes, anorexia, constipation, and polyuria or nocturia (Table 1). As physical manifestations of disease, 4 patients presented with bone tumors and cysts and 2 had palpable neck masses on initial examination. The average preoperative serum calcium level was 17.1 mg/dL (4.28 mmol/L) (range, 15.0-22.2 mg/dL [3.75-5.55 mmol/L]).

The average time between admission to this institution and parathyroidectomy for the entire group was 5 days (range, 1-29 days). All patients underwent vigorous preoperative medical treatment followed by surgical intervention. Twenty-seven patients (63%) underwent bilateral neck exploration. In this group, 21 had 1 parathyroid adenoma, 4 had MGD, and 2 had parathyroid carcinoma. The remaining 16 patients (37%) un-

Table 1. Medical History and Presenting Symptoms in Patients With Hypercalcemic Crisis

	No. (%) of Patients
Medical history	
Hypertension	16 (37)
Weight loss	12 (28)
Hyperparathyroidism	10 (23)
Renal insufficiency	9 (21)
Kidney stones	7 (16)
Previous parathyroidectomy	5 (12)
Hypercalcemia	4 (9)
Bone disease	4 (9)
Malignancy	2 (5)
Hematuria	2 (5)
Peptic ulcer disease	1 (2)
Presenting symptoms	
Musculoskeletal complaints	27 (63)
Fatigue	19 (44)
Mental status changes	15 (35)
Anorexia	12 (28)
Polyuria, nocturia	12 (28)
Constipation	11 (26)
Nausea, vomiting	9 (21)
Abdominal pain	6 (14)
Cardiac	5 (12)
Depression	4 (9)
Pancreatitis	3 (7)
Thirst	1 (2)

derwent limited parathyroidectomy guided by intraoperative PTH. Of this group, 15 had a single hypersecreting gland and 1 patient had MGD. The majority of abnormal parathyroid glands were located in orthotopic locations of the neck. Two patients had ectopic parathyroid glands; 1 had an adenoma in the right thymus while the other had a right intrathyroidal adenoma.

Of the 43 patients with hypercalcemic crisis, 42 (98%) underwent successful parathyroidectomy and showed improvement of symptoms and normalization of calcium levels in the immediate postoperative period. One comatose patient had a history of sporadic primary hyperparathyroidism unsuccessfully treated by parathyroidectomy at an outside hospital. After a delayed transfer to this medical facility, a large right inferior parathyroid gland was removed with normalization of serum calcium level. His mental condition did not improve and he developed a lower gastrointestinal tract hemorrhage. His family refused further operative intervention, and he died 14 days later.

Five patients (12%) experienced transient hypocalcemia after parathyroidectomy and required temporary treatment with calcium and cholecalciferol supplementation. There were no cases of permanent hypoparathyroidism. Postoperative complications occurred in 8 individuals (19%). Four (9%) developed mild renal insufficiency and did not require dialysis after discharge from the hospital. Two (5%) developed postoperative pneumonia successfully treated with antibiotics. One patient (2%) developed transient palsy of the right recurrent laryngeal nerve after excision of an enlarged right inferior parathyroid gland intimately attached to this

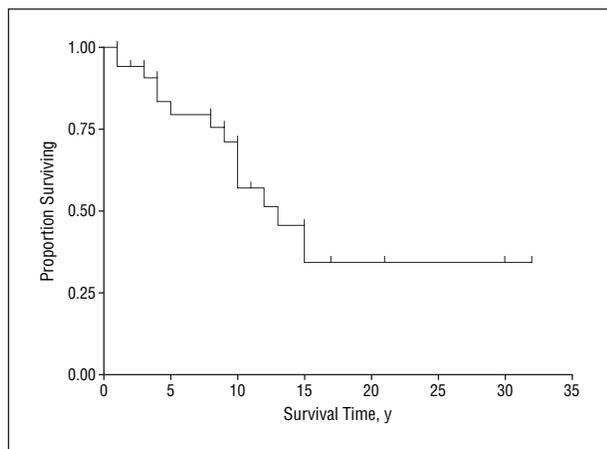


Figure. Kaplan-Meier survival curve for 42 patients with hypercalcemic crisis. Median survival was 11.7 years.

Table 2. Univariate Analysis of Clinical Prognostic Factors for Survival

Factor	Hazard Ratio (95% CI)	P Value
Age	1.05 (1.01-1.09)	.02
Sex (female)	1.17 (0.45-3.02)	.75
Hypertension	1.16 (0.46-2.96)	.75
Weight loss	1.74 (0.64-4.68)	.27
Anorexia	1.43 (0.50-4.06)	.50
Bone or muscle pain	0.55 (0.16-1.91)	.34
Constipation	1.15 (0.41-3.22)	.79
Fatigue	0.59 (0.21-1.67)	.32
Mental confusion	2.03 (0.77-5.38)	.15
Muscle weakness	0.98 (0.38-2.53)	.97
Polyuria, nocturia	1.03 (0.37-2.90)	.95
Surgery delay (≥ 72 h)	0.98 (0.36-2.67)	.96
Preoperative calcium level (≥ 18 mg/dL)	1.17 (0.33-4.18)	.81
No. of symptoms (≥ 3)	1.20 (0.48-3.05)	.69

Abbreviation: CI, confidence interval.

SI conversion factor: To convert calcium to millimoles per liter, multiply by 0.25.

nerve. Another patient had a myocardial infarction 3 days after parathyroidectomy, but recovered after triple coronary bypass surgery 4 months later.

Six months or more of follow-up data were available for 27 patients who underwent parathyroidectomy. Of this group, 26 (96%) were eucalcemic. One patient with a previous cervical spinal fusion and unilateral neck exploration for a single enlarged gland had persistent hypercalcemia. She underwent successful removal of a second enlarged gland and remained eucalcemic until her death 9 years later. Of the 16 patients who did not have long-term follow-up, 12 were eucalcemic in the immediate postoperative period. One patient died postoperatively and another died 2 months after surgery. Three other patients, including 1 treated for parathyroid carcinoma, were eucalcemic 2, 4, and 5 months after surgery.

There were 3 recurrences (7%), occurring at 7, 58, and 265 months. Cervical exploration in the first patient showed an enlarged atypical parathyroid gland adher-

ent to the right recurrent laryngeal nerve. His calcium levels remained normal until 7 months later, when he underwent a repeated resection for parathyroid carcinoma. After an additional resection for cancer recurrence, he died of this disease 4 years after his initial diagnosis. The second patient with a history of right parathyroid adenoma excision underwent a second neck exploration and resection of a left inferior parathyroid adenoma. He presented again at 58 months with recurrent disease confirmed by elevated intact PTH and serum calcium levels. After another operation involving the removal of a large right inferior gland, he remained eucalcemic until his death 15 years after his initial surgery. The third patient, with a history of hyperparathyroidism, vitamin D-resistant rickets, and severe bone disease, underwent subtotal parathyroidectomy and remained eucalcemic until she had a recurrence 22 years after initial surgery. An additional hypersecreting parathyroid gland located in the left carotid sheath was removed during a fourth neck exploration. The patient subsequently did well and remained eucalcemic.

As shown in the **Figure**, the overall median survival of this group was 11.7 years (95% confidence interval, 9.2-NE [not estimable]). The mean serum calcium level was 9.1 ± 0.9 mg/dL (2.28 ± 0.23 mmol/L) at a median follow-up of 48 months. One patient was excluded from this survival analysis because of no follow-up data, and 6 were eventually lost to follow-up but were included in the overall survival analysis. Eighteen patients confirmed to be still alive had a long-term median follow-up of 96 months (range, 2-373 months). The mean postoperative serum calcium level in this group was 9.4 ± 0.6 mg/dL (2.35 ± 0.15 mmol/L) at a median follow-up of 62 months. Although 18 patients had died at a median survival of 6.7 years (range, 2 weeks to 14.8 years), all had been eucalcemic (mean serum calcium level, 9.1 ± 1.2 mg/dL [2.28 ± 0.30 mmol/L]) at a median follow-up of 36 months. Three died of myocardial infarction, 2 of metastatic disease (parathyroid and breast cancer), and 1 of cerebral stroke. The cause of death for the other 12 remains unknown.

A univariate analysis showed that only younger age was significantly ($P = .02$) associated with a better survival (**Table 2**). Other variables, including female sex, hypertension, and bone or muscle pain, were not statistically significant and did not influence long-term survival. Surgical delay (≥ 72 hours), preoperative calcium level (≥ 18 mg/dL [≥ 4.50 mmol/L]), and number of preoperative symptoms (≥ 3), when adjusted for age, did not have a significant effect on long-term survival.

COMMENT

Hypercalcemic crisis is an acute condition that, if left untreated, may cause death from cardiac arrest, renal failure, or complications of coma. The treatment of this syndrome involves rehydration, lowering of serum calcium level, and removal of hyperfunctioning parathyroid tissue. Emergent parathyroidectomy has been shown to provide the best postoperative course for patients in hypercalcemic crisis.⁹ The immediate success of parathyroidectomy in the treatment of this condition has been

well described in earlier reports.^{8-11,13-16} However, the extended outcome of patients presenting with the severe manifestations of hypercalcemia remains unknown. This is the first report, to our knowledge, to demonstrate that hypercalcemic crisis treated by definitive parathyroidectomy results in excellent long-term survival with continued normal parathyroid function.

A 4% incidence of hypercalcemic crisis was observed in 1055 patients treated by parathyroidectomy at this institution during a 35-year period. The most common presenting symptom was musculoskeletal complaints, followed by fatigue, mental status changes, and polyuria or nocturia, which is consistent with other reports.¹³⁻¹⁵ With respect to medical history, hypertension was most common, followed by weight loss, renal insufficiency, and kidney stones, all suggesting an underlying chronicity of hyperparathyroidism. Although previous studies suggest a 25% incidence of acute pancreatitis associated with hypercalcemic crisis,¹⁵ only 3 patients (7%) were treated for this syndrome in our series. Similarly, while some report that an offending parathyroid gland is palpable in up to 50% of patients presenting with hypercalcemic crisis, only 2 (5%) in this study had a palpable neck mass on initial examination.¹⁴

Although preoperative medical measures may bring about temporary improvement, definitive treatment for hypercalcemic crisis remains primarily surgical. While some medical reports^{11,16} suggest emergent operative intervention is not justified, this study, among others,^{8,9,13,14} demonstrates that prompt parathyroidectomy is achieved with minimal morbidity and mortality and excellent postoperative results. In this study, there was 1 postoperative death; in this case, surgical consultation and treatment were obtained only after prolonged therapy, when the patient's condition had severely deteriorated.

Forty-two patients (98%) underwent successful parathyroidectomy and achieved eucalcemia in the immediate postoperative period. Operative success was shown in 26 (96%) of 27 patients followed 6 months or longer. There was 1 operative failure (2%) in a patient with MGD who underwent a unilateral exploration because of a previous cervical spinal fusion. She underwent an additional excision of a contralateral parathyroid adenoma in a subsequent cervical exploration and recovered uneventfully. The 3 individuals treated for recurrent disease (7%) had underlying causes that included parathyroid carcinoma, vitamin D-resistant rickets, and recurrent hyperparathyroidism of undefined cause.

The 18 patients who remain alive and eucalcemic at last follow-up had a median survival of 8 years, with 1 living 31 years after parathyroidectomy. The 18 patients who died had all been eucalcemic at last median follow-up of 3 years. They survived a median of 6.7 years, with 1 dying of myocardial infarction almost 15 years after his parathyroidectomy. The only significant variable associated with increased long-term survival after parathyroidectomy for hypercalcemic crisis was younger age. Other variables, such as female sex, hypertension, weight loss, bone or muscle pain, mental confusion, polyuria or nocturia, and initial preoperative calcium level, were not significant in survival.

Earlier published reports^{11,16} suggest that the best results in the treatment of hypercalcemic crisis are obtained with medical management with rehydration and calcium-lowering agents, without emergent surgical intervention. In this study, however, there were no significant differences in long-term survival when patients were emergently treated with surgery within 72 hours compared with patients treated for 72 hours or more with medical management after admission to this institution. Early operative intervention for hypercalcemic crisis has provided excellent results in the treatment of these patients.

The findings from this study suggest that parathyroidectomy remains essential in the treatment of hypercalcemic crisis, and operative intervention is the therapy of choice regardless of preoperative serum calcium level or associated surgical risk factors. In preoperative management, rehydration should proceed simultaneously with calcium-lowering treatments. Even when patients are dehydrated in severe stages of this disease, operative intervention will achieve excellent results and long-term cure. Performed skillfully and promptly in a well-prepared patient, parathyroidectomy is most effective in the treatment of hypercalcemic crisis, resulting in continued normal parathyroid function and excellent long-term survival.

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