

Primary hyperparathyroidism presenting as hypercalcemic crisis: Twenty-year experience

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ABSTRACT

Context: To study hyperparathyroid-induced hypercalcemic crisis (HIHC). **Aims:** We see very advanced cases of primary hyperparathyroidism (PHPT) and therefore, we sought to determine the incidence of HIHC in our surgically-treated PHPT patients, clinical presentation, and short- and long-term results with the use of bisphosphonate therapy and expeditious parathyroidectomy over a 20-year period at a single institution. **Settings and Design:** Retrospective review of PHPT patients at Department of Endocrine Surgery, a tertiary care referral center. **Materials and Methods:** Retrospective review of 177 patients of advanced PHPT who underwent parathyroidectomy at a single institution from 1989 to 2010. All patients with serum calcium ≥ 14 mg/dl (≥ 3.5 mmol/l) were included in HIHC group. **Statistical Analysis:** Analysis of variance (ANOVA) was used to determine differences between groups. Data is expressed as mean \pm standard error of the mean (SEM); *P* values less than 0.05 were considered significant. **Results:** We observed a higher incidence of HIHC ($n = 37$, 21%) with higher incidence of pancreatitis ($n = 5$, 13.5%). Crisis patients had heavier (6,717 mg) glands. Use of bisphosphonate therapy in seven crisis patients resulted in quicker lowering of serum calcium (mean: 4.5 vs 14.6 days in other crisis patients, $P = 0.027$) permitting early surgery. The incidence of postoperative hypocalcemia was not higher in these patients. Although the parathyroid adenoma was common pathology in both the groups, the incidence of parathyroid carcinoma was higher in crisis group (10.8%). Outcome with regards to postoperative eucalcemia was similar in both groups. **Conclusions:** Crisis patients are at risk of developing pancreatitis. Bisphosphonate therapy has the potential to quickly lower the serum calcium permitting early surgery without added risk of postoperative hypocalcemia. Successful and sustained eucalcemia with excellent long-term survival is possible with use of bisphosphonates and semi-emergent, focused parathyroidectomy.

Key words: Bisphosphonate, hypercalcemic crisis, parathyroidectomy, primary hyperparathyroidism

INTRODUCTION

Sporadic hyperparathyroidism and advanced malignancy are the two most common causes of hypercalcemic crisis. Hypercalcemic crisis is an uncommon but not a rare complication of primary hyperparathyroidism (PHPT). Patients usually have profound hypercalcemia

(serum ≥ 14 mg/dl (≥ 3.5 mmol/l)) along with rapid deterioration of central nervous system, cardiac, gastrointestinal, and renal functions.^[1] A review of hyperparathyroid crisis in 1956 mentioned a mortality of 93% which decreased to 14% in recent reviews.^[2-5] Prompt recognition and aggressive measures to reduce serum calcium levels are responsible for dramatic reduction in morbidity and mortality seen in recent series. However, there are concerns about life-threatening cardiac arrhythmias when severe hyperparathyroid-induced hypercalcemic crisis (HIHC) is not treated promptly.^[6] Expeditious parathyroidectomy has been the cornerstone in the management of these patients and has resulted in excellent short- and long-term outcome.^[1] Use of bisphosphonates therapy was suggested as a bridge to elective parathyroidectomy.^[7] We see very advanced

Access this article online

Quick Response Code:



Website:
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DOI:
10.4103/2230-8210.131763

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cases of hyperparathyroidism and therefore, we sought to determine the incidence of hypercalcemic crisis in our surgically treated hyperparathyroid patients, clinical presentation, and short- and long-term results with the use of bisphosphonate therapy and expeditious parathyroidectomy over a 20-year period at a single institution.

MATERIALS AND METHODS

This is a retrospective analysis of 177 patients of sporadic PHPT operated between 1989 and 2010. For our analysis HIHC was defined as symptoms and signs of acute calcium toxicity with a corrected calcium level >14 mg/dl. All patients were optimized with rehydration and calciuresis with selective use of bisphosphonates. Injection pamidronate 60 mg was given intravenously as slow infusion over 4 h. Before 1998, bilateral neck exploration was the operative procedure of choice; after 1998 focused parathyroidectomy was the operation of choice. Routine intraoperative parathyroid hormone (IOPTH) monitoring was introduced only in the year 2010.

Postoperatively, the patients were monitored for manifestations of hypocalcemia with daily serum calcium measurements. Those with hypocalcemia were managed with oral vitamin D and oral calcium supplements. In patients with acute manifestations of hypocalcemia (positive Trousseau's and/or Chvostek's sign) and/or severe biochemical hypocalcemia (serum calcium \leq 7.5 mg/dl), intravenous calcium infusion was given. Histopathological findings were reviewed in 31 patients of HIHC with adenoma and compared with 21 age and gender matched controls of adenoma without HIHC. All the histopathology slides of cases as well as controls were reviewed by two pathologists and following parameters were noted:

- Microcystic pattern defined as small cystic spaces within the adenoma-filled with proteinaceous material
- Intracytoplasmic vacuoles defined as multiple small vacuoles in the cytoplasm of each cell
- Thick fibrous bands traversing within the adenoma referred to as intraglandular fibrosis, and
- Thickening of the capsule.

Statistical Package for Social Sciences (SPSS)-16 (SPSS, Chicago, IL) was used to analyze the variables and analysis of variance (ANOVA) was used to determine differences between groups. Data is expressed as mean \pm standard error of the mean (SEM); *P* values less than 0.05 were considered significant.

RESULTS

Out of 177 patients operated for PHPT, 37 patients (21%) had HIHC [Table 1]. Though the clinical parameters are similar in both groups, more of crisis patients presented with pancreatitis (13.5 vs 5.7%) as compared to noncrisis patients (*P* = 0.01) [Table 2].

All HIHC patients were treated with saline and loop diuretics, and 7/37 (18.9%) were treated with additional pharmacological agents like bisphosphonates.

The average time taken to achieve a decrease in serum calcium level to the desired range of 11-12 mg/dl was 4.5 days (range 2-7 days) in crisis patients in whom bisphosphonate was used in contrast to 14.6 days (range 3-30 days) required in crisis

Table 1: Demographic, biochemical, and densitometric profile in crisis and noncrisis patients

Demographic, biochemical, and densitometric characteristics (Mean \pm SD/SEM)	Crisis, n=37	Noncrisis, n=140	<i>P</i> value
Age, years \pm SD	39 \pm 15	40 \pm 14	0.43
Sex, n (%)			
Male	12 (32)	42 (30)	0.77
Female	25 (68)	98 (70)	
Duration of symptoms, months \pm SEM	56 \pm 12	47 \pm 4	0.16
S. calcium (mg/dl) \pm SD	15.14 \pm 1.06	11.79 \pm 1.24	0.0001
S. phosphorus, inorganic (mg/dl) \pm SD	2.3 \pm 0.5	2.5 \pm 0.7	0.57
S. iPTH (pg/ml) \pm SEM	890.33 \pm 163.7	801.30 \pm 68.87	0.51
S. alkaline phosphatase (U/l) \pm SEM	1017.8 \pm 207.6	1006.1 \pm 113.3	0.47
S. creatinine (mg/dl) \pm SD	1.4 \pm 0.6	1.2 \pm 0.6	0.87
S. 25 (OH) vitamin D (ng/ml) \pm SEM	16.32 \pm 2.48	13.98 \pm 1.18	0.29
BMD at distal forearm (T score) \pm SD	-3.05 \pm 1.64	-3.45 \pm 2.18	0.62
BMD at hip (T score) \pm SD	-2.05 \pm 1.42	-2.47 \pm 1.71	0.50
BMD at lumbar spine (T score) \pm SD	-2.22 \pm 1.63	-2.60 \pm 1.83	0.26

SD: Standard deviation, SEM: Standard error of the mean, S.: Serum, iPTH: Intact parathyroid hormone, BMD: Bone mineral density

Table 2: Presenting symptoms in crisis and noncrisis patients

Presentation	Crisis n=37 (%)	Noncrisis n=140 (%)	<i>P</i> value
Bone pain and fracture	30 (81)	108 (77)	0.76
Proximal muscles weakness	30 (81)	96 (68)	0.18
Fatigue	31 (83)	95 (67)	0.15
Mental status changes	11 (29)	26 (18)	0.21
Kidney stones	9 (24)	25 (17)	0.40
Nephrocalcinosis	7 (19)	13 (9)	
Pancreatitis	5 (13)	8 (5)	0.01
Hypertension	9 (24)	28 (20)	0.71
Palpable neck mass	11 (29)	23 (16)	0.86

patients in whom bisphosphonate was not used ($P = 0.027$). Fifty-four percent underwent bilateral exploration and 29.7% underwent focused parathyroidectomy [Table 3]. Thirty-one (83.7%) had adenoma, two (5.4%) hyperplasia, and four (10.8%) had carcinoma. Majority of adenomas were found at eutopic locations. Twelve patients (32.4%) experienced symptomatic hypocalcemia requiring intravenous (IV) calcium gluconate infusion for a median period of 6 days (range: 3-8 days), 3/7 (42.8%) in bisphosphonate use and 9/30 (30%) in non-bisphosphonate use. IV calcium infusion was required for a median period of 4 days (range 2-10 days) in 73 (52%) noncrisis PHPT patients. Of 37 patients with HIHC, 35 (94.6%) patients underwent successful parathyroidectomy and achieved eucalcemia. Only two patients (5.4%) failed to achieve eucalcemia; one of these patients was lost to follow-up while other underwent reexploration and was found to have multiglandular hyperplasia. At a mean (\pm SEM) follow-up of 2.5 ± 2.9 years (range: 1-13 years) there was only one case of recurrence. This is a case of parathyroid carcinoma that had needle track recurrence 5 years after parathyroidectomy. On long-term follow-up there were three mortality (8.1%) in crisis patients compared to two in noncrisis group (1.4%). One patient expired in perioperative period due to pancreatitis and septicemia, another patient was of parathyroid carcinoma that succumbed to cerebral metastasis, while in the third patient cause of death was unknown. Both the patients in noncrisis group died as a result of end-stage renal disease.

Histopathological evaluation revealed unique features in adenoma of HIHC patients compared to noncrisis patients [Table 4 and Figures 1 and 2]. Chief cell microcystic pattern was observed in 18/31 (58%) patients with HIHC and 5/21 (23.8%) of control group ($P = 0.049$). Similarly, intraglandular fibrosis was observed in 23/31 (74.2%) patients with HIHC and 2/21 (9.5%) of control group ($P = 0.00001$). Same observation was made regarding the capsular thickening in 13/31 (41.9%) patients with HIHC and 1/21 (4.8%) of control group ($P = 0.001$).

DISCUSSION

Hypercalcemic crisis is an unusual state of progressive and marked hyperparathyroidism producing anorexia, vomiting, dehydration, decreased renal functions, deterioration of mental status, confusion, coma, and if untreated, death. The incidence of HIHC varies in literature from 1.6 to 6%.^[3,8] However, we found an unusually high incidence of 21% of HIHC in our patients; this could perhaps be explained by the fact that we see very advanced cases of hyperparathyroidism and HIHC might be the reflection of natural history of untreated hypercalcemia.

Table 3: Operative and histopathological data in crisis and noncrisis patients

Operative and pathological features	Crisis, n=37 (%)	Noncrisis, n=140 (%)	P value
Bilateral neck exploration	20 (54.0)	55 (39.2)	0.006
Focused parathyroidectomy	11 (29.7)	78 (55.7)	
Unilateral neck exploration	5 (13.5)	6 (4.2)	
Focused parathyroidectomy conversion*	4 (10.8)	6 (4.2)	
Mediastinal exploration	1 (2.7)	1 (0.7)	
IOPHT monitoring	5 (13.5)	21 (15)	0.820
Single adenoma	31 (83.7)	120 (85.7)	0.084
Double adenoma	0	4 (2.8)	
Atypical adenoma	0	5 (3.5)	
Hyperplasia	2 (5.4)	8 (5.7)	
Carcinoma	4 (10.8)	3 (2.1)	
Gland weight (mg) \pm SEM	6,717 \pm 1,265	4,848 \pm 630	0.173
Gland size (cm) \pm SD	3.32 \pm 1.31	2.83 \pm 1.32	0.052

*All the patients under this group were included in bilateral neck exploration. SEM: Standard error of mean, SD: Standard deviation, IOPHT: Intraoperative parathyroid hormone

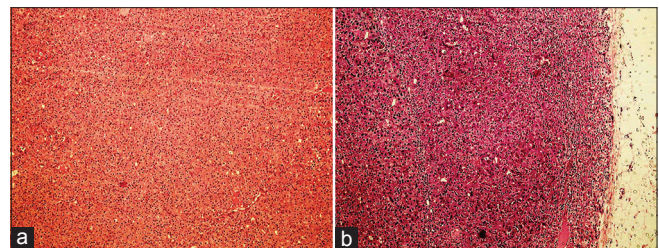


Figure 1: Histopathological findings of parathyroid adenoma in patients (control) with primary hyperparathyroidism without hyperparathyroidism-induced hypercalcemic crisis (HIHC). (a) Adenoma: Microphotograph showing absence of microcystic pattern, intracytoplasmic vacuoles, and intraglandular fibrosis (H and E, $\times 100$ magnification), (b) Adenoma with capsule: Microphotograph showing thin capsule of parathyroid adenoma. There is absence of microcystic pattern, intracytoplasmic vacuoles, and intraglandular fibrosis (H and E, $\times 100$ magnification)

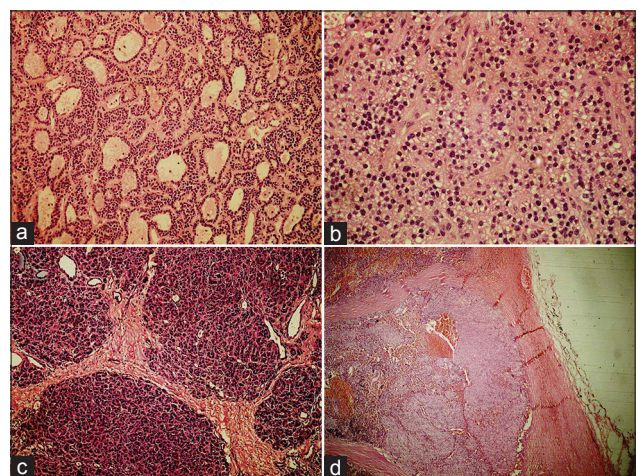


Figure 2: Unique histopathological findings of parathyroid adenoma in patients with HIHC. (a) Microcystic pattern: Dilated follicles forming cysts (H and E, $\times 200$), (b) Intracytoplasmic vacuoles: Cells of parathyroid adenoma showing intracytoplasmic vacuoles (H and E, $\times 400$), (c) Intraglandular fibrosis: Thick fibrous bands traversing within the tumor (H and E, $\times 100$), (d) Intraglandular fibrosis with thick capsule: Thick fibrous bands traversing within the tumor surrounded by thick fibrous capsule (H and E, $\times 100$)

Table 4: Histopathological features

Histopathological features	Microcystic pattern, n (%)			Intracytoplasmic vacuoles, n (%)			Intraglandular fibrosis, n (%)			Capsular thickening, n (%)		
	Absent	Focal	Present	Absent	Focal	Present	Absent	Focal	Present	Absent	Focal	Present
Crisis n=31	10 (32.3)	3 (9.7)	18 (58.1)	10 (32.3)	5 (16.1)	16 (51.6)	6 (19.4)	2 (6.5)	23 (74.2)	14 (45.2)	4 (12.9)	13 (41.9)
Noncrisis n=21 (controls)	13 (61.9)	3 (14.3)	5 (23.8)	11 (52.4)	5 (23.8)	5 (23.8)	19 (90.5)	0	2 (9.5)	20 (95.2)	0	1 (4.8)
P value	0.049			0.133			0.00001			0.001		

All patients had solitary parathyroid adenoma in both crisis and noncrisis group

The most common presenting symptom was either bone disease (81%) and/or nephrolithiasis (43%). Patients however may have severe symptoms of HIHC such as renal failure, acute pancreatitis, and mental changes. Thirteen patients (35%) had acute presentations as follows: Acute pancreatitis ($n = 5$), predominantly gastrointestinal symptoms like severe constipation, epigastric pain, recurrent vomiting, and dyspepsia ($n = 4$) and predominantly renal symptoms like polyuria, polydipsia, dehydration, and oliguria ($n = 4$). Remaining 24 (65%) patients had features of PHPT, but no acute manifestation of hypercalcemic crisis.

A study from the south India found 13% patients had pancreatitis in PHPT and all had significantly high mean serum calcium of 13.2 mg/dl compared to PHPT patients without pancreatic disease (11.8 mg/dl).^[9] Two similar study from the north India found pancreatitis in 6.8 and 14.6% in the PHPT patients.^[10,11] We would like to make a specific mention of pancreatitis associated with crisis. Though recent studies have mentioned low rate of pancreatitis (4-7%), we observed a higher incidence (13.5%) of pancreatitis.^[1,8,12]

Conservative management strategy for HIHC includes rapid intravascular volume expansion with isotonic saline solution, diuretics like frusemide to induce calciuresis, followed by semi-urgent or expeditious parathyroidectomy. Hypercalcemic crisis requires a special accelerated strategy and requires improvement within hours. When hypercalcemia reaches a critical level, these organs are at risk for decompensation. Polyuria may develop into oliguria/anuria, which can be lethal; psychiatric symptoms may progress to somnolence and finally coma; tachyarrhythmias and cardiac arrest may occur. Even though the medical treatment may rapidly bring down the serum calcium levels, definitive treatment is parathyroidectomy.

Though there is no single calcium level which can be considered to be safe before taking these patients of HIHC to surgery, we and our anesthetists would like the calcium

levels to be around 12 mg/dl prior to surgery. Ziegler noted that there is a risk of life-threatening cardiac arrhythmias when severe hypercalcemia is not treated preoperatively.^[6] Hence, it is imperative that the time required to achieve this level be as short as possible.

As such there is no specific guideline for bisphosphonate use in HIHC, most of recommendations based on accepted practice and clinical experience. The role of bisphosphonate therapy as a bridge to elective parathyroidectomy has been explored by only one series.^[7] The authors treated six HIHC patients with IV pamidronate 60-90 mg and one patient with IV zoledronic acid 4 mg to normalize serum calcium before surgery. The average interval between presentation and operation was 8 days (range 3-11 days).^[7]

In another series where authors did not use bisphosphonate, the average time between admission and parathyroidectomy was 5 days (1-29 days).^[1] We used bisphosphonates in seven patients (injection pamidronate 60 mg) and the average interval between presentation and desirable preoperative serum calcium of 11-12 mg/dl was 4.5 days (2-7 days) as compared to 14.6 days (3-30 days) in crisis patients without bisphosphonate use ($P = 0.027$). The mechanism of action of bisphosphonates in HIHC patients can be assumed to be similar to the effect of bisphosphonates on malignancy-induced hypercalcemia. Pamidronate may be given in 60-90 mg doses IV infusion with maximal response at 90 mg over 2-4 h. It causes decrease in calcium levels within 24 h. Zoledronic acid is the newer bisphosphonate agent which is more potent and can be administered in smaller doses: 4 mg over 15 min infusion. Thus bisphosphonates, can be used to optimize HIHC patients and may help in planning early surgery with excellent outcome.

However, there are some concerns regarding the possibility of increased incidence of postoperative hypocalcemia following the use of bisphosphonates in these patients. In a series of Phitayakorn and McHenry, six of eight patients developed hypocalcemia and the authors concluded that use of bisphosphonates medications preoperatively may

be a contributory factor to the severity of postoperative hypocalcemia.^[7] However, we did not observe higher incidence of postoperative hypocalcemia in patients whenever bisphosphonates was used preoperatively. Postoperative calcium level in crisis patient with or without prior use of bisphosphonates showed no significant difference (8.0 ± 0.6 vs 8.0 ± 1.2 mg/dl). There are only few studies examining the optimal treatment of post-parathyroidectomy hypocalcemia. Most recommendations are based upon accepted practice or clinical experience. A policy of prophylactically starting them on oral vitamin D and oral calcium will avoid any profound hypocalcemia.

The aggressive treatment of hypercalcemia should be accompanied by a short diagnostic program. Localization should include a high resolution ultrasonography of neck and Sestamibi imaging. If two are concordant, one can go for minimally invasive or focused parathyroidectomy. After 1994, focused parathyroidectomy was routinely performed at our institution. Introduction of focused parathyroidectomy has really altered the management of hypercalcemic crisis. Because of lesser operative time, smaller incision, and lesser perioperative pain; the anesthetist, patient, and endocrinologist are reassured and agree for a prompt parathyroidectomy with excellent outcome.

Consistent with other reports, crisis patients had significantly larger glands.^[8] However, unlike other series, the incidence of ectopic location especially mediastinal was low in our series.^[8] Schweitzer *et al.*, noted that up to 28% of adenoma in their patients of HIHC may be ectopic.^[13]

The most common pathological finding in HIHC is a solitary parathyroid adenoma. Parathyroid carcinoma is a rare cause of PHPT (<1%), but can be seen in about 5% cases of HIHC.^[7,14] We observed an incidence of 10.8% of parathyroid carcinoma in our HIHC patients compared to 2.1% in non-HIHC PHPT patients. With a mean follow up of 2.5 years, 35 patients remained eucalcemic. Operative failure was seen only in two patients. Thus, early operative intervention provided excellent short- and long-term results.

The histopathological analysis of parathyroid tumors of HIHC may display some unique features which include necrosis, fibrosis, extensive hemorrhage, microcystic pattern, and presence of intracytoplasmic vacuoles.^[15] Various authors have suggested that hemorrhage within an intact parathyroid gland may precipitate hyperparathyroid crisis.^[15-18] However, we are in agreement with Starker *et al.*, who suggested that presence of intracytoplasmic vacuoles is a significant finding and that these PTH-filled vacuoles

may lyse, releasing the hormone and causing increased serum calcium levels.^[15]

CONCLUSION

We believe that prompt recognition of HIHC and treatment with rehydration and forced saline diuresis along with bisphosphonates followed by a semi-emergent focused parathyroidectomy (when imaging is concordant) should be the standard of care in HIHC patients. This will ensure excellent short- and long-term outcome in a life-threatening condition that is uncommon but not rare.

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Cite this article as: Singh DN, Gupta SK, Kumari N, Krishnani N, Chand G, Mishra A, *et al.* Primary hyperparathyroidism presenting as hypercalcemic crisis: Twenty-year experience. *Indian J Endocr Metab* 2015;19:100-5.

Source of Support: Nil, **Conflict of Interest:** None declared.