의학석사 학위논문

Hypercalcemic Crisis in Patients with Primary Hyperparathyroidism

원발성 부갑상선 기능 항진증 환자에서 고칼슘 혈증 위기에 대한 임상적 고찰

2020 년 2 월

서울대학교 대학원

외과학 전공

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Safa Abdelgadir Musa Hamid의 석사 학위논문을 인준함

2020년 1월

위 원 장 _____ (인)

부 위 원 장 _____ (인)

위 원 _____ (인)

Hypercalcemic Crisis in Patients with Primary Hyperparathyroidism

By
Safa Abdelgadir Musa Hamid

Thesis

Submitted to the Faculty of Graduate School of the Seoul National University in Partial Fulfillment of the Requirements for the Degree of Master of Medicine in Surgery

January 2020
Approved by Thesis Committee :

Chair _____(Seal)
Vice Chair. _____(Seal)
Examiner. _____(Seal)

Abstract

Safa Abdelgadir Musa
Degree of Master of Medicine in Surgery
The Graduate School
Seoul National University

Introduction: A hypercalcemic crisis (HC), also called parathyrotoxicosis or parathyroid storm, is a complication of primary hyperparathyroidism (PHPT) and it can lead to death if it is not recognized and treated in time. Identifying the association of the preoperative biochemical values and pathological data that can lead to the development of HC could be helpful in avoid life-threatening complications. Up to now, it remains unclear which PHPT patients are more likely to develop HC. Thus, we tried to identify the association between preoperative biochemical values and pathological data and the incidence of HC in patients with PHPT.

Methods: This study is a retrospective descriptive cohort study. A total of 106 patients who underwent parathyroidectomy were recruited into the study from January 2010 to December 2018 at Seoul National University Hospital. We defined HC as patients who needed hospitalization with symptoms of calcium intoxication comprising bone pain, fatigue, gastrointestinal (GI) symptoms such as abdominal pain, vomiting and nausea, renal stones, altered mental status, acute pancreatitis, cardiac arrhythmias, hypertension and acute renal failure.

Results: The incidence of HC in the present study was 11/106 patients (10.3%). Crisis patients were more likely to have higher preoperative calcium level (median 12.5mg/dl vs. 12mg/dl, P=0.02) and parathyroid carcinoma (9% vs. 0.00%, P= 0.01) compared to non-crisis patients. In multivariable logistic regression analysis, we found that higher preoperative calcium level (OR 8.7 per 1 mg/dl increase, 95% CI 1.03 – 74.2, P=0.04) and parathyroid double adenoma (using radiological findings) (OR 1.6, 95% CI 1.02 – 2.5,

P=0.04) could predict HC in PHPT independently. We also found that patients with preoperative calcium levels greater than 11.5 mg/dl are more likely to develop HC.

Conclusion: Our results indicate that preoperative calcium and parathyroid double adenoma (using radiological findings) are important in predicting HC in patients with PHPT and considering this knowledge will allow us to perform early surgical operations to avoid the potential complications of HC.

Keyword: Calcium, hypercalcemia, hypercalcemic crisis, primary hyperparathyroidism, parathyroidectomy

Student Number: 2018-26119

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INTRODUCTION

Intestinal absorption, renal tubule resorption and bone remodeling process are the main metabolic pathways that maintain the calcium level in our body. Any changes in these paths may lead to hyper or hypocalcemia.[1] The normal range of total calcium concentration in plasma is from 8.5 to 10.5 mg/dl (2.25 -2.55 mmol/l).[2] Of this, 50% is ionized (Ca^{2+}), 40% is bound to proteins (90% binds to albumin), and 10% is complexed with anions (phosphate, citrate, carbonate, sulphate and lactate).[3] Ionized calcium is essential for normal physiological functions and it is mostly controlled by parathyroid hormone (PTH), vitamin D and calcitonin. Vitamin D modulates calcium movement in bone, intestines and kidneys. Calcitonin also has some effect, which gradually decreases the osteoclast activity. Any deviation of calcium levels stimulates numbers of hormonal reactions that lead via the specific receptor parathyroid hormone/parathyroid hormone-related protein type 1 receptor (PTHR1) and vitamin D receptor (VDR) and return the calcium to normal physiological values.[1][3]

Hypercalcemic crisis (HC) is uncommon life-threatening complication that is mostly associated with either overproduction of PTH from diseased parathyroid glands or hypercalcemia due to malignancy.[4] Other causes of hypercalcemia involve renal failure, renal transplantation, endocrinopathies, granulomatous disease and long-term treatment with some medications (vitamin D, retinoic acid, lithium).[1] The genetic causes of hypercalcemia involve familial hypocalciuric hypercalcemia and hypercalcemia that develops as part of multiple endocrine neoplasia (MEN1 and MEN2).[1] The main cause of hypercalcemia in inpatient settings is a malignancy, and the main cause of hypercalcemia in outpatient settings is primary hyperparathyroidism (PHPT).[3]

Patients with HC usually present with elevated serum levels of PTH along with a marked increase in serum calcium level associated with multi-organ dysfunction.[5][6] Ultimately this can lead to death if left untreated.

The clinical presentations of HC can vary , depending on the degree of calcium concentration level and underlying disease, but mostly affecting the central nervous system, cardiac, gastrointestinal tract and renal functions.[3][5][7]

Management of the patients in the parathyroid crisis group consists of emergency measures to acutely decrease serum calcium levels. The first-line therapy consists of volume expansion with normal saline starting with 200-300 mL/hr, which is later adjusted to maintain a urine output of 100-150 mL/hr. Once the patient is rehydrated, a diuretic can be added to decrease calcium resorption in the distal renal tubules, as long as the patient is hemodynamically stable.[4] Other medications can be used in HC cases. Calcitonin at dose 6-8 IU/kg every 6 hours acts rapidly and lowers serum calcium by 1–2 mg/dl but has a side effect of tachyphylaxis by receptor downregulation.[8] Therefore its efficiency is limited to the first 48 hours only. Bisphosphonates such as pamidronate or zoledronic acid take 2-4 days for maximum effects. The effect lasts for several weeks, which can lead to postoperative hypocalcemia.[9] Once the serum calcium level is effectively reduced, urgent parathyroidectomy should be undertaken. Parathyroidectomy will remain the cornerstone of management in HC due to PHPT. Therefore, it is recommended in all patients with classical symptoms of PHPT, and in some patients of asymptomatic PHPT depending on the patient's age, bone density, serum calcium levels, creatinine clearance, 24-hour urine calcium levels, and/or nephrolithiasis on radiological evaluation.[10] The long-term results with a combination of medical and surgical management are excellent.[5][11]

The prevalence of HC due to PHPT reported in the literature varies from 1.6 to 6%. [5][7][12] Ahmad.S et al. mention a study that was done in patients with PHPT in the 1970s that included 882 patients and found only 1.6% presenting in crisis.[12] A more recent study of 1310 patients with PHPT who underwent parathyroidectomy for 40 years reported 6-7% incidence of crisis.[5] Singh. D et al., in a

study that was done between 1989 and 2010, reported 37 patients with a crisis mainly due to PHPT.[11] The majority of patients were more likely to be females (65%), in contrast with other studies showing a slightly greater incidence in men, and all age groups were affected, with no specific age pre-dominance. [5][13]

The most common presenting hypercalcemic symptom was either bone disease and/or renal stone. Patients, however, may have other severe symptoms of HC such as acute renal failure, acute pancreatitis (anorexia, dyspepsia, vomiting, nausea and abdominal pain)[11] and mental changes (confusion, poor concentration, irritability, lethargy and coma).[13][14] In recent studies, kidney dysfunction is found to be present in approximately 17-16% of cases. In mild symptomatic cases of PHPT, significant renal dysfunction is infrequently noted. In contrast, moderate to severe symptomatic PHPT is frequently associated with renal impairment, and renal function usually deteriorates over time if left untreated.[15] As expected, an increase of PTH is associated with a higher risk of developing end-stage renal disease due to PHPT. The acute effects of HC on renal function are less well understood. In a case series of 34 patients presenting with HC, the mean preoperative creatinine level was significantly higher than that observed in non-crisis patients with PHPT.[16] However, after parathyroidectomy, both groups' creatinine levels returned to normal, indicating that the severe renal impairment observed in HC is reversible. In none of the cases was the use of renal replacement therapy noted.[15] In addition, mental alternation was noticed to be more significant in the HC patients. This observation has been also reported by many studies which have noticed central nervous system dysfunction (poor concentration, confusion and coma) as a clinical feature of crisis patients.[13][14][17] In a retrospective study of 177 patients of PHPT who had parathyroidectomy from 1989 to 2010 in India, the authors found that 13 patients (35%) had acute presentations as follows: acute pancreatitis (n=5), predominantly GI symptoms like severe constipation, epigastric pain, recurrent vomiting and dyspepsia (n=4) and renal symptoms like polyuria, polydipsia, dehydration and oliguria (n=4), whereas the remaining 24 (65%) patient had features of PHPT, but no acute manifestation of HC.[11] In contrast, recent studies have mentioned the low rate of acute pancreatitis.

A study from South India found (13%) of patients had pancreatitis in PHPT and all had significantly high serum calcium of 13.2 mg/dl compared to PHPT without pancreatic disease and the calcium level was 11.8 mg/dl.[18] Also, cardiovascular manifestations such as shortened QT interval with increased susceptibility to arrhythmias, including heart block and ventricular arrhythmias are known complications of HC. In one retrospective review of 67 patients presenting with HC, only two patients (3%) suffered from cardiac arrhythmias.[19] However, in a similar study of 34 patients presenting with HC, no patients demonstrated evidence of cardiac arrhythmia.[16] Most of the other reports of HC induced cardiac arrhythmia are annotated in case reports. A review of this shows that the presence of significant cardiac arrhythmia associated with HC can be highly variable, including tacky-brady syndrome, ventricular tachycardia, ventricular fibrillation, and proximal trio-ventricular block.[15]

The most common pathological findings in HC is a solitary parathyroid adenoma, whereas parathyroid carcinoma is a rare cause, comprising less than 1% of cases.[9] In a retrospective study of 1754 patients who had parathyroidectomy in the USA from 1991 to 2009, most of the patients with HC display single parasitoid adenoma, although multiglandular hyperplasia was observed in 10.5% of patients. They also found that parathyroid carcinoma was the cause of HC in 4.5% of patients.[19]

Treatment modalities for HC such as hydration, bisphosphonates, calcitonin and loop diuretics have been used for treatment. Bisphosphonates such as Pamidronate are used commonly with 60-90 mg intravenous infusion administrated over two hours.[1] There are no specific guidelines for bisphosphonate use in HC, with most of the recommendations being based on accepted practice and clinical experience. There are some concerns regarding the possibility of an increased incidence of postoperative hypocalcemia following the use of bisphosphonates in these patients. In a series of studies by Phitayakorn and McHenry, six of eight patients developed hypocalcemia and the authors concluded that the use of bisphosphonate medications preoperatively may have been a contributory factor to the severity of postoperative hypocalcemia.[9] Hypercalcemic caused by vitamin D intoxication is rare and mainly in neonatal or infancy. Dominant symptoms are dehydration, as a consequence of vomiting, and weight loss.

Laboratory examination reveals hypercalcemia, hypercalciuria (urinary calcium/creatinine ratio mmol/mmol>0.5), low serum PTH levels and nephrocalcinosis.[20] Hypercalcemia may also be observed in patients treated with high doses of retinoic acid. The active form of the vitamin (all-trans-retinoic acid) activates osteoclasts with a subsequent increase in bone resorption and calcium release into the circulation. Variability around the lowest dosage of vitamin A known to cause hypercalcemia is quite large and the threshold of vitamin A toxicity has not been accurately defined to date. Hypercalcemia can also complicate the long term therapy with thiazide diuretics via increasing reabsorption in the kidneys.[1] In a study carried out in the USA in 2017, to identify the drugs induce hypercalcemia in PHPT cases, patients with crisis were unlikely to be taking hormonal therapy compared with those patients without crisis. During the study period, vitamin D supplements were not associated with HC. [21]

Gurrado et al. reported that mortality is 100% if expeditious parathyroidectomy for HC is not performed.[22] Surgery for HC is unlike most of the parathyroid surgeries, which are elective, whereas parathyroidectomy for HC is urgent.

It remains unclear at present which PHPT patients are at greater risk of developing HC. Thus, identifying an association between preoperative biochemical values and pathological data that can lead to developing HC would allow us to do an early surgical intervention in these patients to avoid any potential life-threatening complications associated with HC.

Patients and Methods

This is a retrospective descriptive cohort study performed on 106 patients who underwent parathyroidectomy from January 2010 to December 2018 at Seoul National University Hospital. We defined HC as patients who needed hospitalization with symptoms of calcium intoxication, comprising bone pain, fatigue, GI symptoms such as abdominal pain, vomiting and nausea, renal stone, altered mental status, acute pancreatitis, cardiac arrhythmias, hypertension and acute renal failure. We excluded patients less than 18 years old or patients who had previously had parathyroid surgery, or patients with secondary or tertiary hyperparathyroidism. Then all patients will be classified into two groups: crisis group and non-crisis group. We gathered information on the age at diagnosis, gender, body mass index (BMI), clinical symptoms, past medical history, preoperative blood tests including calcium, ionized calcium, phosphate, PTH, alkaline phosphatase, vitamin D, creatinine, 24-hours urine calcium, size of any tumor and pathological data. The postoperative assessment includes calcium level, ionized calcium and PTH level. Patients underwent surgery for one, two or subtotal parathyroidectomy and the pathology was classified as single adenoma, double adenoma, atypical adenoma, hyperplasia or carcinoma by the specialist.

Statistical analysis

Continuous variables are presented as medians with the interquartile range (IQR) and were analyzed with the Mann–Whitney U test due to a lack of normality. Categorical variables are described as frequencies with percentages and were analyzed with the chi-square test. Logistic regression analysis was applied to identify the association between preoperative biochemical values and pathological data and the incidence of HC in patients with PHPT. We performed a univariate logistic regression analysis to identify the relationship between predictors and the main outcome of interest. The following variables were

considered as potential predictors of HC: age, gender, duration of symptoms, preoperative PTH, preoperative alkaline phosphatase, preoperative 24-hour urine calcium, preoperative creatinine, preoperative vitamin D, preoperative phosphate, GI symptoms, acute pancreatitis, renal stone, fatigue, bone pain, parathyroid hyperplasia, parathyroid carcinoma, parathyroid adenoma, parathyroid atypical adenoma and size of the tumor. Multivariate logistic regression analysis was used for these same variables with a significant P value = <0.05 to predict the risk factors in crisis patients. We calculated the cut-off value for HC by using receiver operating characteristic curve or ROC curve.

A probability P value < 0.05 was considered statistically significant. All data were processed using the Statistical Package for the Social Sciences (SPSS) statistics for Windows version 25. Data was presented in the form of tables.

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Results

There were 11 (10.3%) patients with HC and 95 (89.6%) patients without HC. Two of the eleven (18.2%) HC patients were hospitalized because of renal stone, another two (18.2%) patients had bone pain, and three patients (27.3%) had GI symptoms such as abdominal pain, vomiting and nausea. Two (18.2%) patients had physical fatigue and two (18.2%) patients had acute pancreatitis. The majority of the patients were female (71%) with a median age of 59 years (Table 1). We also found female patients were (63%) more likely to get HC compared to males ($P < 0.001$) (Table 2). There was a significant difference between the preoperative calcium value in the crisis and non-crisis groups. Patients with crisis had higher median preoperative calcium level (12.5mg/dl vs 12mg/dl, $P < 0.001$) than non-crisis patients (Table 2). However, there was no significant difference between age, preoperative PTH level, preoperative 24-hour urine calcium level, preoperative vitamin D level, preoperative phosphate level, preoperative alkaline phosphatase level, preoperative creatinine level and preoperative calcium level in both groups compared with the non-crisis group.

Table 1. The general characteristics of the study population

Characteristics of the study patients;	Overall patients N (%) IQR	Reference range
Age at diagnosis (median)	59 (48-68)	
Gender: Female Male	 75 (71%) 31 (29%)	
Preoperative calcium level, median (IQR)(mg/dl)	12 (11-12.7)	8.8-10.2
Preoperative ionized calcium level, median (IQR)(mmol/l)	1.5 (1.48-1.76)	1.1-1.35
Preoperative PTH level, median (IQR)(pg/dl)	174 (116-288)	10-65
Preoperative phosphate level, median (IQR)(mg/dl)	2.6 (2.1-3.0)	2.4 - 4.1
Preoperative vitamin D level, median (IQR)(ng/ml)	16.70 (11.7-22)	20 - 50
Preoperative alkaline phosphatase level, median (IQR)(U/l)	26 (17.24-4.98)	44 - 147
Preoperative creatinine level, median (IQR)(mg/dl)	0.8 (0.65-1.0)	0.84 - 1.21

IQR: Interquartile range. PTH: Parathyroid hormone

Table 2. Demographic, biochemical characteristics in crisis and non-crisis patients

Characteristics	Non-crisis (N=95)	Crisis (N=11)	P-value
Age, years median (IQR)	58	61	0.07
Sex, n (%)			0.001
Female	66 (69%)	7 (63%)	
Male	29 (30%)	4 (36%)	
Preoperative biochemical values median (IQR)			
Calcium level, median (IQR)(mg/dl)	12 (11-13.5)	12.5 (11.2-13)	0.02
Ionized calcium, median (IQR) (mmol/l)	1.61 (1.48-1.81)	1.62 (1.46-1.68)	0.26
PTH level, median (IQR)(mg/dl)	169 (109-326)	166 (90-258)	0.93
Phosphate level, median (IQR)(mg/dl)	2.7 (2.1-2.8)	2.5 (2.1-2.6)	0.13
Creatinine level, median (IQR)(mg/dl)	0.76 (0.63-1.01)	0.73 (0.64-0.89)	0.53
24-hour urine calcium level, median (IQR)(mg/24hr)	281(176-417)	404 (222-450)	0.89
Alkaline phosphates level, median (IQR)(mg/dl)	24.3 (15-38)	19.2 (16-40)	0.13
Vitamin D level, median (IQR)(ng/ml)	16 (11.1-22.6)	15.9 (11-21)	0.99

IQR: Interquartile range. PTH: Parathyroid hormone.

Our pathological data revealed that HC due to parathyroid double adenoma was present in 18.2% of cases (P=0.008) and parathyroid carcinoma present in 9% of cases (P=0.01) whereas the remaining patients displayed a single parathyroid adenoma (72.7%). There was no significant difference in the rate of single adenoma or hyperplasia or atypical adenoma between two groups. The median tumor size in crisis patients was (1.9 cm vs 2 cm, P=0.53) comparing with non-crisis patients (Table 4).

Table 3. Pathological data in crisis and non-crisis patients.

Pathological data	Non-crisis (N=95)	Crisis (N=11)	P-value
Single adenoma, n (%)	87 (91.6%)	8 (72.7%)	0.29
Double adenoma, n (%)	2 (2.1%)	2 (18.2%)	0.008
Atypical adenoma, n (%)	3 (3.2%)	0 (0.0%)	0.55
Hyperplasia, n (%)	5 (5.3 %)	0 (0.0%)	0.43
Carcinoma, n (%)	0 (0.0%)	1 (9%)	0.01
Tumor size (cm)	2 (1.2-2.4)	1.9 (1.2-2.5)	0.53

IQR: Interquartile range.

We included additional results in our study and we found that the single tumor present in nine cases (9.7%, P=0.52) and multiple tumors was present in two cases (15.4%, P=0.52) in crisis patients.

Table 4. Radiological data in in crisis and non-crisis patients

Additional results	Non-crisis (N=95)	Crisis (N=11)	P-value
Single tumor	84 (90.3%)	9 (9.7%)	0.52
Multiple tumor	11 (84.6%)	2 (15.4%)	0.52

In univariate logistic regression analysis (Table 5) we found the preoperative calcium level was significant with P value = 0.05 and parathyroid double adenoma had P value = 0.05

Table 5. Univariable analysis of variables to identify risk factors for HC in patients with PHPT.

Univariate analysis				
	OR	95% CI		P-value
Age	1.04	0.00	0.008	0.07
Gender	0.45	0.12	1.61	0.22
Preoperative calcium level	1.72	1.12	2.64	0.01
Preoperative PTH level	0.99	0.99	1.02	0.61
Preoperative alkaline phosphatase level	0.96	0.92	1.01	0.17
Preoperative 24-urine calcium level	0.99	0.99	1.003	0.78
Preoperative creatinine level	2.98	0.25	34.4	0.38
Preoperative vitamin D level	0.98	0.91	1.06	0.73

Preoperative phosphate level	0.50	0.12	2.009	0.32
Parathyroid hyperplasia	0.00	0.00	0.00	0.99
Parathyroid carcinoma	1910	0.00	0.00	0.99
Parathyroid single adenoma	0.65	0.12	3.37	0.60
Parathyroid double adenoma	6.81	1.003	46.28	0.05
Parathyroid atypical adenoma	0.00	0.00	0.00	0.99
Size of tumor	0.93	0.45	1.94	0.86
Single tumor	0.58	0.11	3.38	0.53
Multiple tumor	1.69	0.32	8.89	0.53

GI: Gastrointestinal, PTH: Parathyroid hormone, CI: Confidence interval, OR: Odd ratio.

In multivariate logistic regression analysis (Table 6), we found that higher preoperative calcium level (OR 8.7 per 1 mg/dl increase, 95% CI 1.03 – 74.2, P=0.04), parathyroid double adenoma (using radiological findings) (OR 1.6, 95% CI 1.02 – 2.5, P=0.04) could predict HC in PHPT independently.

Table 6. Multivariate analysis of risk factors for HC in a patient with PHPT

Multi variables analysis				
	OR	95% CI		P value
Preoperative calcium level	8.75	1.03	74.25	0.04
Parathyroid double adenoma (using radiological findings)	1.61	1.02	2.54	0.04

GI: Gastrointestinal, CI: Confidence interval, OR: Odd ratio.

By using receiver operating characteristic curve or ROC curve we calculated the cut-off value for HC. We found that patients with preoperative calcium more than 11.5mg/dl are more likely to develop HC.

Table 7. The cut-off value of HC

Cut-off value for HC	Cut-off value	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Preoperative calcium level	11.5	0.81	0.52	(0.52, 0.85)

AUC: Area under the Curve, CI: Confidence interval

Discussion

Hypercalcemic crisis is also called parathyrotoxicosis or parathyroid storm and is a rare complication of PHPT. Affected individuals develop severe hypercalcemia that is life-threatening. The importance of early medical and surgical treatment in HC patients has been well established. With appropriate management, HC patients can recover completely and remain eucalcemic at long-term follow up.

However, the symptoms of HC can be vague. Crisis patients may present with non-specific symptoms such as fatigue, weakness, abdominal pain/vomiting and mental alternation instead of presenting with classical symptoms such as bone disease or renal stone. Many previous studies have used a plasma concentration of calcium of 14 mg/dl or 15 mg/dl as a lower limit of HC definition.[5][11][16][19] However, crisis patients may present with symptoms and signs of calcium intoxication below this limit. Thus, unlike previous studies that use plasma calcium level alone to define HC, we defined HC based on the clinical manifestation of calcium intoxication.

In our study, we found a higher incidence of HC (10.3%) compared to other studies of (1.6-6%) [5][7][12], which can be explained by the fact that our hospital received very advanced cases of PHPT. Our patient's ages ranging from 48 to 68 years old with the median age of 59 years old. Most of the patients (85%) were 45 years old or more, although we found an increase in age did not increase the risk of HC (P=0.07). We also found female patients were (63%) more likely to get HC compared to males (P <0.001). This is contrary to the study which states that crisis patients were more likely to be male.[7][17]

The preoperative serum calcium level was significantly greater among crisis patients. An increase in calcium level leads to an increase in the risk of developing HC. This result is consistent with the Lowell. et al. study that has shown having elevated calcium was associated with an increase of HC among the PHPT patients.[21] In contrast to the findings of Lowell et al., we found the P-value of preoperative PTH was not significant (P=0.9) in crisis patients compared with the non-crisis group. The most common pathological finding in HC is single parathyroid adenoma, which presents in (81.8%) of cases.

Parathyroid carcinoma is uncommon cause of PHPT with less than 1% incidence noted in previous studies.[5][11] Although the total number of patients in crisis and non-crisis groups were small, the percentage of cases of parathyroid carcinoma was significantly greater (P=0.01) consistent with the 5% rate reported in the recent review of the literature that included selected series and case reports over 29-years.[9] Also, double adenoma was noticed to be significantly more prevalent in crisis patients (18.2%, P=0.008).

This study has shown a strong association between higher preoperative calcium level and parathyroid double adenoma (using radiological findings) and the incidence of HC in patients with PHPT. We also found that patients with preoperative serum calcium more than 11.5 mg/dl are more likely to develop HC.

This study has several limitations. 1) It is a retrospective study. 2) The small number of patients in our adult cohort may have limited our ability to accurately analyze the association between preoperative biochemical values and multiplicity of a tumor and HC in patients with PHPT. 3) We exclude calcium impact medications from our analysis because there was a lot of missing data. 4) Seoul National University Hospital is a tertiary referral center; therefore, referral bias may have caused the overestimation of the prevalence of HC in our data. Also, it's important to note that the previous studies had different study designs. They had different definitions of HC and the different sizes of the study population, which makes our results difficult to compare to other studies in the literature.

According to our knowledge, few studies exist where the definition of HC depends on the clinical presentation of calcium intoxication rather than the calcium level alone. Our study was the only study in Asia that used this definition. We thought this definition is more useful for identifying the risk for HC in PHPT instead of just using serum calcium level to define HC. Lastly, the small number of patients in our study made our results somewhat fragile, so we suggest further that investigations with a large number of PHPT patients are needed to achieve more robust data and conclusions.

Conclusions

Our results indicate that HC was present in 10.5% of PHPT patients. We found that preoperative calcium and parathyroid double adenoma (using radiological findings) are important in predicting HC in patients with PHPT. We also found that patients with preoperative serum calcium levels greater than 11.5 mg/dl are more likely to develop HC. Therefore, the initial evaluation of patients with general symptoms consistent with HC must include not only careful history and physical examination focusing on the clinical manifestation of HC but we also need to focus on preoperative calcium level and likely multiplicity of a tumor. Considering this knowledge will allow us to perform early surgical operations to avoid the potential complications of HC. It is important to mention that our total number of patients in both groups was small so we suggest that further studies focusing on HC with larger numbers of patients with PHPT are needed.

References

[1] I. Žofková, “Hypercalcemia. Pathophysiological aspects,” Physiol. Res., vol. 65, no. 1, pp. 1–10, 2016.

[2] R. B. Payne and B. E. Walker, “Serum-Calcium,” Lancet, vol. 313, no. 8128, p. 1248, 1979.

[3] K. L. M. Courtney M. Townsend, Jr, R. Daniel Beauchamp, Mark Evers, Sabiston textbook of surgery: biological basis of modern surgical practice. 2017.

[4] S. Ameerudden and X. He, “Management and surgical treatment of parathyroid crisis secondary to parathyroid tumors: Report of four cases,” Int. Med. Case Rep. J., vol. 4, no. 1, pp. 59–66, 2011.

[5] J. Cannon, J. I. Lew, and C. C. Solórzano, “Parathyroidectomy for hypercalcemic crisis: 40 years’ experience and long-term outcomes,” Surgery, vol. 148, no. 4, pp. 807–813, 2010.

[6] T. D. Sala, S. Mureşan, R. Roman, A. Lazăr, R. Ion, and I. Paşcanu, “Hypercalcaemic Crisis Due to Primary Hyperparathyroidism: Report of Two Cases,” J. Crit. Care Med., vol. 5, no. 1, pp. 34–39, 2019.

[7] R. L. Payne and C. W. Fitchett, “Hyperparathyroid Crisis: Survey of the Literature and a Report of Two Additional Cases.,” Ann. Surg., vol. 161, pp. 737–747, 1965.

[8] C. B. Isselmuiden and R. R. Faden, “The New England Journal of Medicine Downloaded from nejm.org on January 31, 2011. For personal use only. No other uses without permission. Copyright © 1992 Massachusetts Medical Society. All rights reserved.,” vol. 326, 1992.

[9] R. Phitayakorn and C. R. McHenry, “Hyperparathyroid Crisis: Use of Bisphosphonates as a Bridge to Parathyroidectomy,” J. Am. Coll. Surg., vol. 206, no. 6, pp. 1106–1115, 2008.

[10] J. K. Kim et al., “The prevalence of primary hyperparathyroidism in Korea: A population-based analysis from patient medical records,” Ann. Surg. Treat. Res., vol. 94, no. 5, pp. 235–239, 2018.

[11] D. N. Singh et al., “Primary hyperparathyroidism presenting as hypercalcemic crisis: Twenty-year experience,” Indian J. Endocrinol. Metab., vol. 19, no. 1, pp. 100–105, 2015.

[12] S. Ahmad, G. Kuraganti, and D. Steenkamp, “Hypercalcemic crisis: A clinical review,” Am. J. Med., vol. 128, no. 3, pp. 239–245, 2015.

[13] E. Sarfati, L. Desportes, D. Gossot, and C. Dubost, “Acute primary hyperparathyroidism: Experience of 59 cases,” Br. J. Surg., vol. 76, no. 9, pp. 979–981, 1989.

[14] L. A. Fitzpatrick, “Acute Primary Hyperparathyroidism,” Parathyroids Basic Clin. Concepts Third Ed., vol. 82, pp. 401–408, 2014.

[15] T. C. Brown, J. M. Healy, M. J. Mcdonald, J. H. Hansson, ; Courtney, and E. Quinn, “Heart Block and Acute Kidney Injury Due to Hyperparathyroidism-Induced Hypercalcemic Crisis,” 2014.

[16] W. Beck, J. I. Lew, and C. C. Solórzano, “Hypercalcemic crisis in the era of targeted parathyroidectomy,” J. Surg. Res., vol. 171, no. 2, pp. 404–408, 2011.

[17] C. A. Wang and S. W. Guyton, “Hyperparathyroid crisis. Clinical and pathologic studies of 14 patients,” Ann. Surg., vol. 190, no. 6, pp. 782–790, 1979.

[18] J. J. Jacob et al., “Does hyperparathyroidism cause pancreatitis? A south Indian experience and a review of published work,” ANZ J. Surg., vol. 76, no. 8, pp. 740–744, 2006.

[19] L. F. Starker, P. Björklund, C. Theoharis, W. D. Long, T. Carling, and R. Udelsman, “Clinical and histopathological characteristics of hyperparathyroidism- induced hypercalcemic crisis,” World J. Surg., vol. 35, no. 2, pp. 331–335, 2011.

[20] F. Hmami, A. Oulmaati, A. Amarti, M. L. Kottler, and A. Bouharrou, “Surdosage ou hypersensibilité à la vitamine D?,” Arch. Pediatr., vol. 21, no. 10, pp. 1115–1119, 2014.

[21] A. J. Lowell et al., “Assessing the risk of hypercalcemic crisis in patients with primary hyperparathyroidism,” J. Surg. Res., vol. 217, no. February, pp. 252–257, 2017.

[22] A. Gurrado, G. Piccinni, G. Lissidini, P. Di Fronzo, F. Vittore, and M. Testini, “Hypercalcaemic crisis due to primary hyperparathyroidism - A systematic literature review and case report,” Endokrynol. Pol., vol. 63, no. 6, pp. 494–502, 2012.

국문 초록

서론: 부갑상선 중독증 또는 부갑상선 폭풍이라고 불리는 고칼슘혈증위기(Hypercalcemic crisis)는 원발성 부갑상선기능항진증(primary hyperparathyroidism,PHPT)의 합병증으로 발생할 수 있고 적절한 진단과 치료를 받지 않으면 사망으로 이끌 수 있다. 원발성 부갑상선기능항진증 환자에서 고칼슘혈증의 위기의 위험인자는 명확하지 않다. 그래서 본 연구를 통해서 원발성 부갑상선기능항진증 환자에서 고칼슘혈증위기의 발생과 임상병리학적 양상과의 연관성을 확인하고자 하였다.

방법: 2010 년 1 월부터 2018 년 12 월까지 서울대학교병원에서 부갑상선 절제술을 받은 10 명의 환자를 연구대상으로 하였다. 고칼슘혈증 위기로 뼈 통증, 피로, 복통, 구토 및 메스꺼움, 신장결석, 혼수, 급성 췌장염, 심장 부정맥, 고혈압 및 신부전으로 입원이 필요한 경우로 정의하였다.

결과: 고칼슘혈증의 위기는 106 명의 환자 중 11 명에서 발생하였다. (10.3%). 고칼슘혈증 위기환자는 고칼슘혈증 비위기환자에 비하여 수술 전 칼슘수치가 높게 나타났고 (중값간 12.5mg/dl vs. 12mg/dl, P=0.02) 부갑상선암 발생 빈도도 더 높게 나타났다. (9% vs. 0.00%, P= 0.01). 다변량 로지스틱 회귀분석을 통해 수술 전 칼슘수치가 높은 경우(OR 8.7 per 1 mg/dl increase, 95% CI 1.03 – 74.2, P=0.04)와 부갑상선 이중선종의 경우 (OR 1.6, 95% CI 1.02 – 2.5, P=0.04) 원발성 부갑상선기능항진증에서의 고칼슘혈증위기를 독립적으로 예측할 수 있었다. 또한 수술전의 칼슘수치가 고칼슘혈증의 위기로 진행된 군에서 11.5mg/dl 이 높게 나타났다.

결론: 칼슘수치와 부갑상선 이중선종의 유무가 원발성 부갑상선기능항진증를 가지고 있는 환자에서 고칼슘혈증위기의 위험인자가 될 수 있다는 것을 밝혀 냈고 이점을 고려하여 고칼슘혈증위기의 잠재적인 합병증을 예방하기 위하여 초기 외과수술을 권고 할 수 있다.

주요어: 칼슘, 고칼슘 혈증, 고칼슘 혈증 위기, 부갑상선 기능 항진증, 부갑상선 절제술

학 번: 2018-26119