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Preoperative biochemical values are correlated with adenoma volume, but not predictive factors for hungry bone syndrome in patients with primary hyperparathyroidism

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Abstract

We aimed to investigate correlation between perioperative biochemical values and adenoma volume, the effects of perioperative biochemical values and clinicopathological variables on postoperative hypocalcemia after parathyroidectomy. A retrospective study planned in tertiary university hospital on patients undergone surgery for primer hyperparathyroidism. Preoperative calcium (first, close to surgery, maximum), PTH (first, close to surgery, maximum), alkaline phosphatase (ALP) and phosphorus (P) values, postoperative calcium (early, late), postoperative PTH (early, late), 24-hour urinary calcium calculation, time from the first diagnosis of elevated calcium until surgery, preoperative hypercalcemia treatments, excised parathyroid gland, histopathologic diagnosis, maximum diameter and volume of the excised parathyroid on histopathologic examination, postoperative intravenous calcium supplement were analyzed. 73 patients were included in the study. The median age of the patients was 54 years (range, 18-82), and 83.6% were female. In univariate analysis, patients who were administrated intravenous (IV) calcium supplement had higher preoperative PTH (p=0.024). adenoma volume correlated moderate with preoperative PTH first (r=0.396, p=0.001), preoperative maximum parathormone (r=0.380, p=0.001), preoperative PTH CS (r=0.432, p<0.001) and preoperative first elevated calcium (r=0.240, p=0.041) levels. We conclude that biochemical parameters and adenoma size are not predictive factors in determining the requirement of IV calcium supplement. Preoperative PTH and calcium levels were moderately associated with adenoma volume.

Keywords: Primer hyperparathyroidism, calcium supplement, hypocalcemia, parathormone, adenoma volume, hungry bone syndrome

Introduction

Parathyroid adenoma is the most common cause of primary hyperparathyroidism. Surgical intervention, which aims to eliminate excessive parathormone pressure on calcium metabolism, remains the gold standard in treatment. One of the most important problems faced by clinicians after parathyroidectomy is hypocalcemia. In hungry bone syndrome, which is characterized by dramatic decreases in blood calcium levels, presents with severe symptoms that adversely affect patient comfort. [1]. There are case reports in the literature showing that hypocalcemia causes episodes of psychological illness. [2]. For this reason, studies have focused on revealing the predictive factors of hypocalcemia after parathyroidectomy. Studies with perioperative biochemical variables have shown that high preoperative Ca and PTH levels and rapid decrease in intraoperative PTH may be risk factors for the development of hypocalcemia [3,4]. There is even a study that provides a formula

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to predict the lowest postoperative blood calcium level after thyroid and parathyroid surgery. [5]. While it has been shown in different studies that the size of the excised adenoma may be a predictive factor for postoperative hypocalcemia [6-9], there are also opposing views stating that the size of the adenoma has no effect [10,11].

In this study, we aimed to investigate the effects of preoperative biochemical values, adenoma size (volume), location (parathyroid localization), and time from diagnosis to surgery on the development of postoperative hypocalcemia due to the presence of opposing views. We also investigated the effects of preoperative hypercalcemia treatment on postoperative calcium levels and the requirement of postoperative IV calcium supplement.

Material and Methods

A retrospective study planned to investigate the effects of the excised parathyroid volume, preoperative biochemical values, time from the first diagnosis to surgery, and preoperative hypercalcemia treatments on the development of postoperative hypocalcemia in patients who undergone parathyroidectomy for primary hyperparathyroidism. Tokat Gaziosmanpaşa University Clinical Research Ethics Committee approval was received. The data of patients who undergone parathyroidectomy for primary hyperparathyroidism in Tokat Gaziosmanpaşa University Faculty of Medicine General Surgery clinic between January 2010 and August 2022 were analyzed. Patients above 18 years of age were included in the study. Patients in whom the specimen was excised piecemeal, malignancy was found on histopathologic examination, data were not available and patients with familial hypocalciuric hypercalcemia were excluded from the study.

Age, sex, 24-hour urinary calcium calculation, time from the first diagnosis of elevated calcium until surgery, preoperative hypercalcemia treatments, excised parathyroid gland, histopathologic diagnosis, maximum diameter and volume of the excised parathyroid on histopathologic examination, postoperative intravenous calcium supplement were recorded. The volume was calculated by using the formula $V=AxBxCx\pi/6$ (Miccoli Formula) for the dimensions given in the histopathologic examination.

Biochemical values

Following values were extracted and analyzed:First high preoperative calcium (mg/dL,pre-op Ca first), parathormone (pg/ml, pre-op PTH first), alkaline phosphatase (U/L, ALP first) and phosphorus (mg/dL, P first).

Maximum preoperative calcium (mg/dL, pre-op Ca max), parathormone (pg/ml, pre-op PTH max) and minimum preoperative phosphorus (mg/dL, P min).

Preoperative calcium close to surgery (mg/dL, pre-op Ca CS), parathormone (pg/ml, pre-op PTH CS), alkaline phosphatase (U/L, ALP CS) and phosphorus (mg/dL, P CS). Postoperative early calcium (mg/dL,post-op early Ca min), parathormone (pg/ml, post-op early PTH).

Postoperative late calcium (mg/dL,post-op late Ca), parathormone (pg/ml, post-op late PTH).

Statistical Analysis

While evaluating the findings of the study, SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Whether the scores obtained from each continuous variable were normally distributed or not were analyzed using descriptive, graphical, and statistical methods. Kolmogorov-Smirnov test was used to test the normality of the scores obtained from a continuous variable with the statistical method. Descriptive statistical methods (number, percentage, median, etc.) were used while evaluating the study data. Comparisons between the two groups in quantitative data were made using the Mann–Whitney U test; Qualitative comparisons between groups were made using Chi-Square tests (Yates's correction and Fisher's Exact Test). The level of relationship between the two continuous variables was examined with Spearman's correlation test. In the study, multivariate logistic regression modeling was used to measure the effect of independent variables on the dependent variable. The results were evaluated within the 95% confidence interval and the significance was evaluated under $p<0.05$. Correlations were considered strong at $r \geq 0.6$, moderate at $0.2 \leq r < 0.6$ and weak at $r < 0.2$.

Results

Totally 73 patients were included in the study. The median age of the patients was 54 years (range, 18-82), and 83.6% were female. When the clinical and pathological features of the disease were examined, the median symptom duration of the patients was 155 days (range, 14-2908), and most of them had adenoma tumor type (97.3%). The maximum pathological diameter of the adenoma was calculated as median 2 cm (range, 0.6-5) and its volume was calculated as median 1.2 cm3 (range, 0.05-26.3). Thyroidectomy surgery was performed in 19 patients (26%) in the same session. IV calcium supplement therapy was applied to 21 patients (28.8%) in the postoperative period. No statistically significant difference was found in the demographic and clinicopathological characteristics of the patients who required IV calcium supplement therapy ($p>0.05$). Demographic and clinicopathologic characteristics of the patients are presented in Table 1.

Univariate Analysis Results

The median preoperative and postoperative biochemical values of the patients are presented in detail in Table 2. There was a statistically significant difference in Pre-op PTH first and early postoperative Ca minimum levels according to IV calcium supplement status. Patients who were administered IV calcium supplement had higher preoperative PTH first ($p=0.024$) and had lower early postoperative Ca minimum ($p<0.001$) levels.

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Table 1. Comparison of demographic and clinicopathological characteristics between research groups

		Postoperative IV Calcium Supplement			
Variables		**All**	**Yes**	**No**	**p-Value**
Number of patients, n(%)		73(100)	21(28.8)	52(71.2)	
Age#		54(18-82)	49(18-82)	55(21-76)	0.166[a]
Sex, n(%)	Male	12(16.4)	3(25)	9(75)	0.999[c]
	Female	61(83.6)	18(29.5)	43(70.5)	
Duration of symptoms (day) #		155(14-2908)	119(14-2069)	186(15-2908)	0.421[a]
Parathyroid localization, n(%)	Right (inferior=35/ superior=3)	38(52.1)	13(34.2)	25(65.8)	0.417[b]
	Left (inferior=35/ superior=3)	35(47.9)	8(22.9)	27(77.1)	
Histopathologic diagnosis	Adenoma	71(97.3)	21(29.6)	50(70.4)	0.999[c]
	Hyperplasia	2(2.7)	0(0)	2(100)	
With thyroidectomy, n(%)		19(26)	6(31.6)	13(68.4)	0.984[b]
Adenoma maximum diameter(cm)#		2(0.6-5)	2(0.7-3.5)	2(0.6-5)	0.425[a]
Adenoma volume (cm3) #		1.2(0.05-26.3)	0.6(0.08-7)	1.2(0.05-26.3)	0.314[a]
Preoperative hidration+diuretics, n(%)		40(54.8)	9(22.5)	31(77.5)	0.297[b]
Preoperative biphosphonates, n(%)		18(24.7)	8(44.4)	10(55.6)	0.133[b]

p>0.05, a:Mann Whitney U Test, b:Yates's correction, c:Fisher's Exact Test, #:median(range)

Table 2. Comprasion of perioperative biochemical values of patients between research groups

	Postoperative IV Calcium Supplement			
	All	**Yes**	**No**	
Variables	**Median(range)**	**Median(range)**	**Median(range)**	**p-Value**
Pre-op Ca first (mg/dl)	11.44(10.62-15.7)	11.6(10.62-15.7)	11.4(10.63-15.35)	0.100
Pre-op Ca-Max.(mg/dl)	11.9(10.68-16.1)	12.48(11-16.1)	11.79(10.68-15.2)	0.055
Per-op Ca CS (mg/dl)	11.4(9.7-15.5)	11.27(9.9-15.5)	11.4(9.7-13.7)	0.190
Post-op early Ca-Min.(mg/dl)	9.10(7.3-11.1)	8.3(7.3-10.67)	9.4(7.9-11.1)	<0.001*
Post-op late Ca (mg/dl)	9.3(6.8-11.2)	9.35(6.8-11.2)	9.3(8.1-10.47)	0.730
Pre-op PTH first (pg/ml)	212(57.24-1566)	260.5(103.1-1566)	174.25(57.24-1174)	0.024*
Pre-op PTH-Max.(pg/ml)	239.5(84.99-1566)	305.8(111.4-1566)	194.8(84.99-1174)	0.066
Per-op PTH CS (pg/ml)	204.1(44.55-1566)	275.45(44.55-1566)	161.25(84.99-1142)	0.119
Post-op early PTH(pg/ml) (n=68)	12.95(1.2-267.4)	12.66(1.78-267.4)	13.01(1.2-135.1)	0.819
Post-op late PTH(pg/ml) (n=58)	58.22(2.9-310)	53.17(9.1-170.9)	58.44(2.9-310)	0.489
Pre-op ALP first (n=59)	108(55-748)	109(55-748)	108(55-3649	0.639
Per-op ALP CS (n=55)	103(47-697)	111.5(55-6979	102(47-260)	0.146
Pre-op P first	2.46(1.68-4.27)	2.37(1.82-3.16)	2.51(1.68-4.27)	0.217
Pre-op P-Min.	2.38(1.13-3.9)	2.35(1.42-3.12)	2.4(1.13-3.99	0.540
Per-op P CS	2.47(1.13-3.9)	2.44(1.42-3.24)	2.47(1.13-3.99	0.622

*p<0.05, Mann Whitney U Test, Pre-op:preoperative, Post-op:postoperative CS: close to surgery

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Table 3. Multivariate regression analysis results

Variables	β	SE	Wald's	OR (95%CI)	p-Value
Post-op early Ca-Min.(mg/dl)	-2.541	0.671	14.33	0.079(0.021-0.294)	<0.001*
Pre-op Ca-Max.(mg/dl)	0.543	0.377	2.080	1.721(0.823-3.602)	0.149
Pre-op PTH first (pg/ml)	0.009	0.007	1.575	1.009(0.995-1.022)	0.209
Pre-op PTH-Max (pg/ml)	-0.009	0.007	1.597	0.991(0.977-1.005)	0.206
Constant	15.177	7.143	4.515	3.90E+6	

*:p<0.05, Multiple Logistic regression, Method=Enter, OR: Odd Ratio, CI:Confidence Interval, SE:Standard error, R2(Nagelkerke)=0.56, Model $\chi 2$=35819, p<0.001, Dependent variable: IV replacement (1=yes, 0=no), Correct classification probability of the model:86.3%, Note:OR and P-value were obtained using multivariate logistic regression analysis model

Table 4. The correlation between study parameters, adenoma volume and perioperative biochemical values

	Adenoma volume (cm3)		Pre-op PTH (pg/ml)	
Variables	**r**	**p-Value**	**r**	**p-Value**
Pre-op PTH first (pg/ml)	0.396	**0.001***	NA	NA
Pre-op PTH-Max.(pg/ml)	0.380	**0.001***	0.952	**<0.001***
Per-op PTH CS (pg/ml)	0.432	**<0.001***	0.867	**<0.001***
Post-op early PTH(pg/ml)	0.088	0.475	0.208	0.089
Post-op late PTH(pg/ml)	0.237	0.073	0.348	**0.008***
Pre-op Ca first (mg/dl)	0.240	**0.041***	0.295	**0.011***
Pre-op Ca-Max.(mg/dl)	0.184	0.120	0.475	**<0.001***
Per-op Ca CS (mg/dl)	0.032	0.787	0.106	0.372
Post-op early Ca-Min.(mg/dl)	0.204	0.084	-0.003	0.981
Post-op late Ca (mg/dl)	-0.107	0.375	0.005	0.965
Pre-op P first	-0.102	0.397	-0.435	**<0.001***
Pre-op P-Min.	-0.184	0.122	-0.425	**<0.001***
Pre-op ALP first	0.157	0.234	0.300	**0.021***

*:p<0.05, r: Spearman's correlation test, NA: not available, CS:close to surgery

In addition, preoperative calcium and parathormone maximum levels were higher in patients requiring IV Ca supplement (p=0.055 and p=0.066), which was close to statistical significance.

Multivariate Regression Analysis Results

Multivariate logistic regression analysis using the enter method was performed, including the variables (Pre-op PTH first and Pre-op PTH-Max; Pre-op Ca-Max and Post-op early Ca-Min) that were statistically significantly or nearly significantly associated with the presence of IV Ca supplement in univariate analyses. According to the results of the regression analysis, the coefficient of determination of the model was R2(Nagelkerke)=0.56. Accordingly, it was found that 56% of the variance in the

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dependent variable was explained by the independent variables. Since the p value in the model (F=35.819, p<0.001) is smaller than the α value, it is determined that the model is significant at 95% confidence level. The correct classification probability of the model was 86.3%. The model correctly predicted the requirement of IV supplement 86% of the time with the biochemical values used. According to the multiple logistic regression model, the only independent variable associated with the requirement of postoperative IV supplement was early postoperative calcium minimum level (OR: 0.079, 95%CI: 0.021-0.294) (Table 3).

Correlation Between Continuous Variables

There was a statistically significant and moderate positive correlation between adenoma volume and preoperative PTH first (r=0.396, p=0.001) (Figure 1), preoperative maximum parathormone (r=0.380, p=0.001) (Figure 2), preoperative PTH CS (r=0.432, p<0.001) (Figure 3) and preoperative first elevated calcium (r=0.240, p=0.041) levels. (Figure 4) From this finding, it was determined that adenoma volume increased as preoperative parathormone and calcium levels increased.

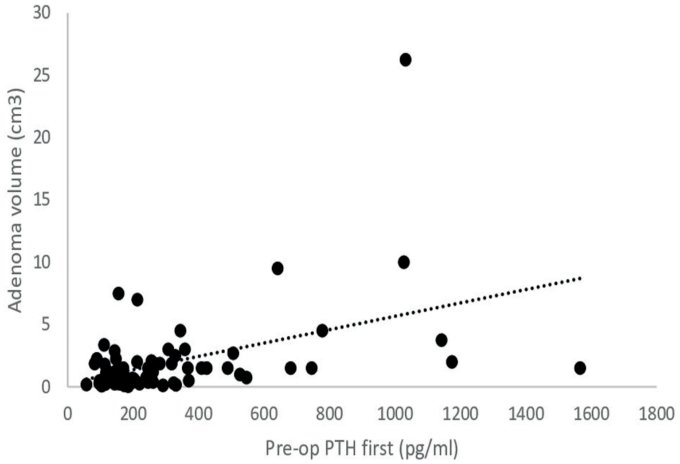

Figure 1. Correlation between adenoma volume and Pre-op PTH first

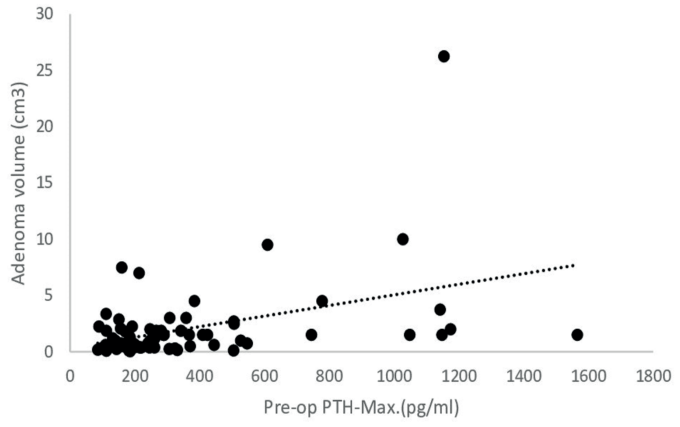

Figure 2. Correlation between adenoma volume and Pre-opPTH max

There was a statistically significant and positive correlation between preoperative parathormone level and preoperative calcium first (r=0.295, p=0.011), preoperative calcium maximum level (r=0.475, p<0.001) and preoperative ALP first (r=0.300, p=0.021), a statistically significant and negative correlation between preoperative parathormone level and preoperative phosphorus first (r=-0.435, p<0.001) and preoperative phosphorus minimum level (r=-0.425, p<0.001). (Table 4)

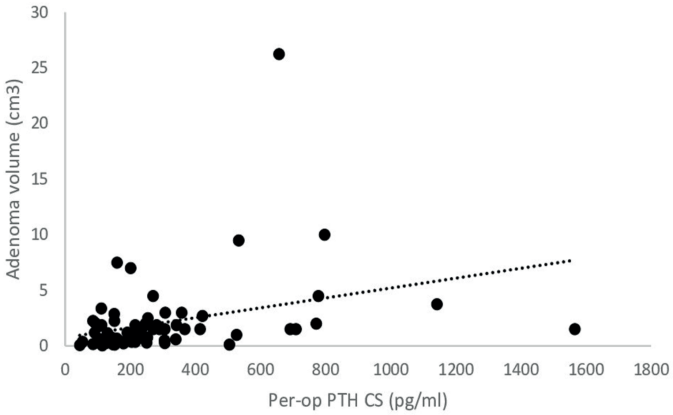

Figure 3. Correlation between adenoma volume and Pre-op PTH CS

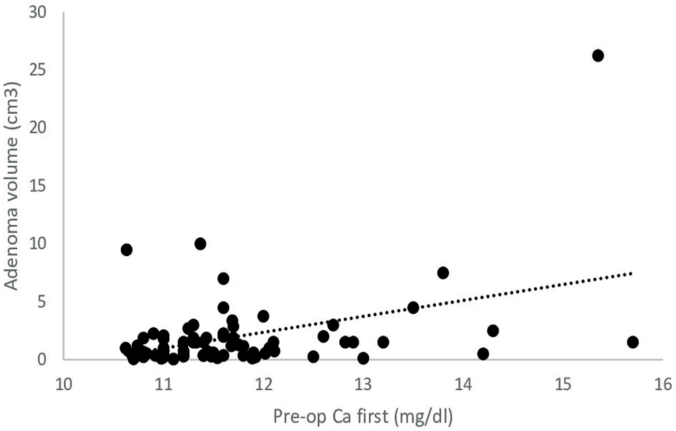

Figure 4. Correlation between adenoma volume and Pre-op Ca first

Discussion

In our study, we found that demographic and clinicopathological data were not effective in determining requirement of intravenous calcium supplement in patients who were operated on for primary hyperparathyroidism. Comparing the patients with and without IV calcium supplement, both groups were similar in terms of age and sex. There was no statistically significant difference between the two groups in terms of the time from the first diagnosis to the operation, the effect of simultaneous thyroidectomy, and preoperative hypercalcemia treatments. In the univariate regression analysis of perioperative biochemical parameters, the PTH level measured at first diagnosis was found to be statistically significantly higher in patients who required IV calcium supplement. Although preoperative maximum calcium levels were higher in IV calcium supplement patients, but not statistically significant. In multivariate regression analysis, these two parameters were not independent factors

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for IV calcium supplement. These results revealed the necessity of close Ca monitoring to determine the requirement of IV calcium supplement. In one study, close Ca monitoring was strongly recommended to prevent hungry bone syndrome after parathyroidectomy. [12]. There is no consensus on the risk factor of preoperative biochemical parameters in the development of hungry bone syndrome. There are studies concluding that preoperative calcium, preoperative PTH, and ALP levels that are 2 times higher than normal levels are predictive factors in hungry bone syndrome [13-15]. In a study comparing patients with and without hungry bone syndrome, no statistically significant difference was observed in terms of preoperative biochemical parameters. [16].The same uncertainty applies to adenoma weight and dimensions. Although the volume of tissue excised in patients with primary hyperparathyroidism greater than 5 cubic centimeters was shown as a risk factor in a review study, it was stated that there was insufficient data on the subject. [17]. In our study, it was revealed that the volume and maximum diameter of the removed parathyroid adenoma were not significant in terms of IV calcium supplement.

In our study, we found that the excised parathyroid volume was moderately correlated with preoperative calcium and PTH levels. A large-series study showed a moderate correlation between adenoma weight and preoperative PTH levels [18,19]. In another large-series study, it was shown that adenoma weight was statistically significantly higher in patients with PTH levels above 150 pg/ml [20].

One of the limitations of our study is that it is retrospective. Due to the retrospective nature of our study, we observed that ALP values were not analysed in some patients. In addition, the fact that histopathological examinations were evaluated by different pathologists during the long study period was another limitation of our study. This may have caused interobserver bias, especially regarding specimen sizes. However, we think that this situation did not affect our results because the averages of the removed parathyroid sizes were similar and small.

In conclusion, we believe that biochemical parameters and adenoma size are not predictive factors in determining the requirement of IV calcium supplement. For this reason, we concluded that close post-operative calcium monitoring is needed to determine the requirement of IV calcium supplement. We also concluded that preoperative PTH and calcium levels were moderately associated with adenoma volume.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
okat Gaziosmanpaşa University Clinical Research Ethics Committee approval was received (no:22-KAEK-216)

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