

Research Article

Predictors of Hypocalcemia in Patients Undergoing Parathyroidectomy with the Diagnosis of Primary Hyperparathyroidism

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Abstract

Objectives: Hypocalcemia is one of the important and potentially dangerous complications seen after parathyroid surgery. The purpose of our study was to determine the predictive factors for hypocalcemia in the postoperative period and to identify the risky patient group.

Methods: 77 patients who underwent parathyroid surgery between January 2014 and July 2018 were included in the study. The patients were divided into four groups on the first postoperative day and on the fourth day in patients with hypocalcemia and normocalcemic cases. Factors predicting hypocalcemia were statistically compared between groups.

Results: The mean age of the patients (F/M: 65/12) was 58.2±11.7 years. The preoperative serum calcium level of patients with hypocalcemia on the first postoperative day was <12.05 mg/dl. The preoperative cut-off values of parathormone >187.5 pg/ml, 25-hydroxy vitamin D (25 OHD) <10.5 ng/ml, phosphorus <2.45 mg/dl, and parathyroid adenoma volume >1.04 cm³ were present in patients with prolonged hypocalcemia on postoperative fourth day.

Conclusion: In the preoperative period, determining the factors to predict postoperative hypocalcemia will reduce the complications due to severe hypocalcemia and shorten the hospitalization time.

Keywords: Parathyroid surgery, postoperative hypocalcemia, primary hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is a hormonal disease that occurs as a result of parathyroid hormone release from one or more parathyroid glands, excessive and uncontrolled. In the laboratory examination, the diagnosis of primary hyperparathyroidism is made by the elevated total and ionized calcium value, the increase of parathormone value and the lack of suppression. Detection of incidental calcium elevations with routine serum calcium scans and increased frequency of radiological imaging methods;

There has been a relative increase in the incidence of PHPT in recent years. PHPT usually affects the kidneys, gastrointestinal tract, central nervous system, cardiovascular system, and musculoskeletal system, and it has many different clinical manifestations.^[1–3]

For all symptomatic patients without contraindications and for many patients with asymptomatic PHPT, the most appropriate treatment is parathyroidectomy. Parathyroidectomy is a surgical procedure that is very easy for an ex-

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perienced endocrine surgeon with a low complication rate. It plays a role in the development of hypocalcemia in transient hypoparathyroidism with the rapid absorption of calcium into the bones in the early postoperative period.^[4] Hypocalcemia with mild symptoms improves within 2-4 days with calcium and vitamin D supplementation. In addition, severe hypocalcemia lasting more than 4 days may rarely develop. Hypocalcemia is the most important reason for prolonging hospital stay in patients undergoing parathyroid surgery.^[5] Prolonged and severe hypocalcemia may cause cardiac arrhythmias, myocardial dysfunction, and pulmonary edema if the necessary precautions are not taken.^[6] The aim of this study was to determine the predictive factors for hypocalcemia in the early postoperative period and to identify patients at risk of severe hypocalcemia after parathyroid surgery.

Methods

Demographic, clinical and laboratory data of patients who underwent parathyroid surgery between January 2014 and July 2018 at Evliya Celebi Training and Research Hospital were retrospectively analyzed. 77 patients were included in the study. Patients with secondary hyperparathyroidism due to chronic renal failure, patients with toxic multinodular goiter or graves disease, those with high calcium or parathormone (PTH) levels after failed parathyroid surgery, and persistent hypoparathyroidism with persistent hypoparathyroidism at the sixth postoperative month were excluded. In the postoperative period, biochemical hypocalcemia was accepted as those with a total calcium level below 8.5 mg/dl. On the first postoperative day, two groups were defined as hypocalcemic and normocalcemic cases. Likewise, after the fourth day, patients were divided into two groups: hypocalcemia and normocalcemic ones. Factors that could predict hypocalcemia were compared between groups.

In our study, data obtained after 10-12 hours of night fasting were used. 25 OHD, parathormone and thyroid stimulating hormone (TSH) chemilumination were determined by immunoassay measurement method (Beckman Coulter DXI-800, Beckman Coulter, Inc. Fullerton, CA 92835 USA). Alkaline phosphatase (ALP), calcium, phosphorus, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride, were measured by Beckman Coulter AU 2700, Beckman Coulter, Inc., Brea, CA 92821 USA. The hemogram is performed with laser-based impedance using an automated blood cell counter (Mindray BC-6800, Nanshan, Shenzhen, PR China). Data from the patient files were recorded by examining the presence of diabetes mellitus, hypertension, nephrolithiasis, and osteoporosis. Simultaneous thyroid surgery information

Table 1. Demographic and clinical features of primary hyperparathyroidism patients

Variables	Data
Patients count, n	77
Sex (F/M)	65/12
Age, years (mean±SD)	58.2±11.7
Diabetes mellitus (n, %)	29, 37.6
Hypertension (n, %)	36, 46.7
Nephrolithiasis (n, %)	24, 31.1
Osteoporosis (n, %)	38, 49.3
Thyroid surgery accompanying parathyroid surgery (n, %)	31, 40.2
TSH, uIU/mL (mean±SD)	1.8±1.1
Free T4, ng/dl (mean±SD)	0.87±0.13
Serum creatinine mg/dl (mean±SD)	0.89±0.25
AST, U/L (mean±SD)	22.1±8.5
ALT, U/L (mean±SD)	21.1±11.6
WBC, 10 ³ /mm ³ (mean±SD)	7.5±2.2
Hemoglobine, g/dl (mean±SD)	13.1±1.6
Hematocrit, % (mean±SD)	39.9±4.3
Platelet, 10 ³ /mm ³ (mean±SD)	262.3±71.6
25- hydroxy vitamine D, ng/ml [median- IQR (min-max)]	11.8–20.1 (4–108)
Fasting blood glukose, mg/dl (mean±SD)	111±33.2
Total cholesterol, mg/dl (mean±SD)	202.3±38
LDL-C, mg/dl (mean±SD)	121.5±31.3
HDL-C, mg/dl (mean±SD)	46.9±12.3
Triglyceride, mg/dl (mean±SD)	177.8±89
Preoperative Ca ²⁺ , mg/dl (mean±SD)	11.7±0.6
Preoperative phosphorus, mg/dl (mean±SD)	2.34±0.5
Parathormone, pg/ml median-IQR (min.-max.)	197–236.5 (77–2568)
Alkaline phosphatase, U/L median-IQR (min.-max.)	108–74 (38–781)
Parathyroid adenoma volume, cm ³ median-IQR (min.-max.)	1.25–1.5 (0.15–20.8)

F: Female, M: Male; SD: Standard deviation; TSH: Thyroid stimulating hormone; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; WBC: White blood cells; IQR: Interquartile range; min.: Minimum; max.: Maximum; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

and parathyroid adenoma dimensions were obtained from pathology reports. The volume of parathyroid adenoma was calculated by the ellipsoid model formula (length x width x height x 0.52).^[7] The study protocol was approved by The Ethics Committee of Kütahya Dumlupınar University.

Statistical Analysis

The statistical analysis of the data was performed using the “SPSS 18.0. All data are summarized by supporting tables and graphs. During the evaluation, descriptive statistical

Table 2. Possible variables for the causes of developing hypocalcemia in the first day postoperatively

Variables	Calcium \leq 8.5 mg/dl (2)	Calcium $>$ 8.5 mg/dl (1)	p
Sex (F/M)	34/3	31/9	0.10
Age, years (mean \pm SD)	56.3 \pm 13.5	59.9 \pm 9.6	0.18
Preoperative Ca, mg/dl (mean \pm SD)	11.5 \pm 0.74	11.8 \pm 0.61	0.03
Preoperative parathormone, pg/ml, median-IQR (min.-max.)	187-236.5 (82-1914)	226-207 (77-2568)	0.75
Postoperative parathormone, pg/ml, median-IQR (min.-max.)	14-19.7 (1-171)	10-14.5 (0.8-48)	0.14
25-hydroxy vitamine D, ng/ml, median-IQR (min.-max.)	10.2-19 (4-71.9)	12.4-26.8 (4-108)	0.15
Alkaline phosphotase U/L, median-IQR (min.-max.)	97-65 (51-781)	118-90 (37-728)	0.70
Preoperative phosphorus, mg/dl (mean \pm SD)	2.4 \pm 0.6	2.3 \pm 0.4	0.40
Thyroid surgery accompanying parathyroid surgery (+/-)	16/21	15/24	0.81
Hemoglobine, gr/dl (mean \pm SD)	12.8 \pm 1.5	13.3 \pm 1.6	0.21
Hematocrit, % (mean \pm SD)	39.2 \pm 4.3	40.6 \pm 4.4	0.15
TSH, uIU/mL (mean \pm SD)	1.81 \pm 1	1.75 \pm 1.2	0.82
Parathyroid adenoma volume, cm ³ , median-IQR (min.-max.)	1.4-2.1 (0.2-20.8)	1.1-1.4 (0.15-9.36)	0.71

F: Female, M: Male; SD: Standard deviation; TSH: Thyroid stimulating hormone; IQR: Interquartile range; min.: Minimum; max.: Maximum.

Table 3. Possible variables for prolonged hypocalcemia reasons for the postoperative fourth day

Variables	Calcium \leq 8.5 mg/dl (2)	Calcium $>$ 8.5 mg/dl (1)	p
Sex, (F/M)	14/4	51/8	0.3
Age, years (mean \pm SD)	58.1 \pm 10.6	58.2 \pm 12.1	0.95
Preoperative Ca, mg/dl (mean \pm SD)	11.8 \pm 0.6	11.6 \pm 0.6	0.25
Preoperative PTH, pg/ml, median-IQR (min.-max.)	482-481 (123-1914)	168-150 (77-2568)	<0.001
Postoperative PTH, pg/ml, median- IQR (min.-max.)	9-15.2 (8-29.8)	12-18 (1-171)	0.35
25-hydroxy vitamine D, ng/ml, median- IQR (min.-max.)	6.1-9 (4-54)	17.6-28.6 (4-108)	0.01
Alkaline Phosphotase, U/L, median-IQR (min.-max.)	128.5-188 (40-781)	106-63 (37-728)	0.61
Preoperative phosphorus, mg/dl (mean \pm SD)	2.1 \pm 0.35	2.43 \pm 0.55	0.01
Thyroid surgery accompanying parathyroid surgery (+/-)	10/8	21/38	0.10
Hemoglobine, gr/dl (mean \pm SD)	12.6 \pm 2	13.2 \pm 1.4	0.23
Hematocrit, % (mean \pm SD)	38.9 \pm 5.6	40.2 \pm 3.9	0.28
TSH, uIU/mL (mean \pm SD)	2.1 \pm 1.4	1.7 \pm 1.0	0.28
Parathyroid adenoma volume, cm ³ , median-IQR (min.-max.)	1.92-2.7 (0.75-9.3)	1.04-1.4 (0.15-20.8)	0.01

F: Female, M: Male; SD: Standard deviation; TSH: Thyroid stimulating hormone; IQR: Interquartile range; min.: Minimum; max.: Maximum.

methods (mean, standard deviation, median, interquartile range, minimum and maximum value), in the same sample group of the quantitative data in the appropriate distribution of pre and post-operation groups in the appropriate distribution, Paired T-test, in groups not showing the appropriate distribution Wilcoxon Signed Rank test was used.

The results were statistically significant at 95% confidence interval at $p < 0.05$. For variables that were thought to be predictors of postoperative hypocalcemia, cut-off values were determined with ROC analysis.

Results

The mean age of 77 patients (F/M: 65/12) included in the study was 58.2 \pm 11.7 years. Demographic and clinical data

of the cases are shown in Table 1. Biochemical hypocalcemia was detected in 48% of the patients on the postoperative first day. The preoperative calcium level was significantly lower in the group with hypocalcemia on the first postoperative day and no significant correlation was found with the other variables (Table 2).

Hypocalcemia extending to the postoperative fourth day was observed in 23.3% of the patients. Preoperative parathyroid hormone and parathyroid adenoma volume were significantly higher in late hypocalcemia postoperatively than in the fourth postoperative day. There was no significant relationship between other variables and late hypocalcemia extending to the fourth day (Table 3).

For the development of hypocalcemia on the first postop-

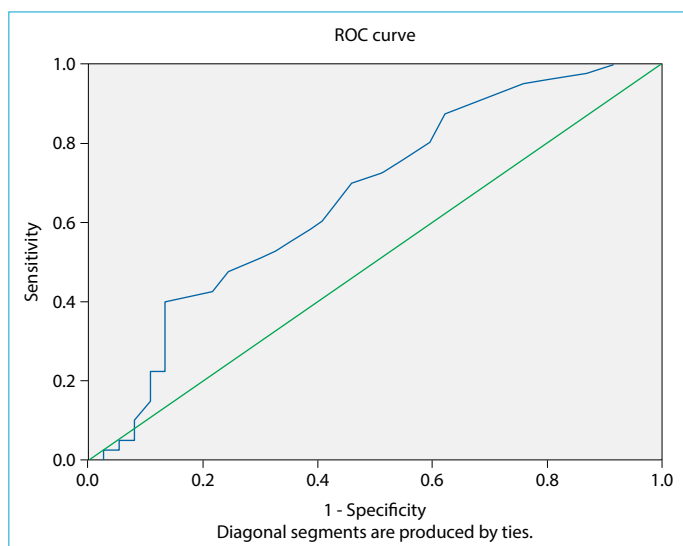


Figure 1. The ROC curve of the preoperative Ca⁺ values in the development of hypocalcemia on postoperative first day.

erative day, the cut-off value of preoperative serum calcium level was <12.05 mg/dl with ROC analysis (40% sensitivity, 86% specificity, AUC=0.663, 95% CI 0.54-0.78, p=0.03) (Fig. 1). In the ROC analysis for the development of hypocalcemia extending to the fourth postoperative day, the cut-off values of the different ones; For preoperative parathormone with 42% sensitivity and 88% specificity >187.5 pg/ml (AUC=0.199 (95% CI 0.079-0.320); p<0.001), preoperative 25 OHD with 64% sensitivity and 70% specificity <10.5 ng/ml (AUC=0.707 (95% CI 0.558-0.856); p=0.01) with 42% sensitivity and 94% specificity for preoperative phosphorus <2.45 mg/dl (AUC=0.678 (95% CI 0.541-0.814); p=0.01) and parathyroid adenoma volume was found to be >1.04 cm³ (AUC=0.339 (95% CI 0.198-0.479); p=0.01) with 82% specificity and 51% sensitivity (Fig. 2).

Discussion

Several mechanisms have been proposed for transient postoperative hypocalcemia. Decreased parathormone secretion from non-adenoma atrophic glands and damage to normal parathyroid glands during surgical dissection may cause postoperative hypoparathyroidism. Another mechanism of hypocalcemia associated with hypophosphatemia and remineralization in the skeletal system is characterized by the hungry bone syndrome.^[7-10]

Hypocalcemia is one of the important and potentially dangerous complications seen after parathyroid surgery.^[11] It may be asymptomatic and may be accompanied by paresthesia, muscle cramps and tetany symptoms.^[12] Calcium plays an important role in ventricular functions. In electrocardiography due to hypocalcemia, prolongation of QT interval, T-wave alternans reflecting the inhomogeneity of

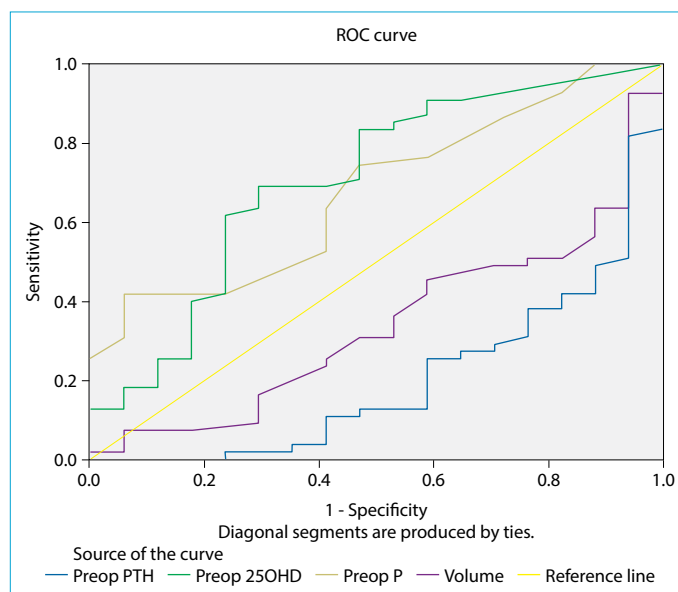


Figure 2. The ROC curve of the preoperative PTH, 25 OHD, phosphorus ve parathyroid adenom volume values in the development of hypocalcemia on postoperative fourth day.

cardiac repolarization may lead to life-threatening serious adverse events such as ventricular arrhythmia and sudden cardiac death.^[13,14]

In addition, hypocalcemia may lead to reversible myocardial dysfunction in the early postoperative period. Case reports have been reported showing that heart failure due to hypocalcemia is improved by calcium replacement.^[15,16] Other serious symptoms include pulmonary edema, laryngospasm, epileptic seizures and cognitive disorders.^[17] Determining the factors that predict hypocalcemia in the postoperative period is important for the findings of severe hypocalcemia.

The sampling time of calcium taken in the early postoperative period varies in studies. In some studies, calcium levels were observed in the first 6 hours or 24 hours, in others in the morning of the day after surgery.^[7,18,19] In our surgical clinic, calcium level is observed in the first 8 to 12 hours after surgery. The incidence of hypocalcemia in the first 24 hours was 37% and 23.3% in two different studies and 38.4% in a recent study.^[11,20,21] In our study, biochemical hypocalcemia was detected in the postoperative first day in contrast to other studies (48%).

Preoperative calcium levels were found to be significantly lower in the hypocalcemia group but there was no significant relationship with other variables. In many studies evaluating hypocalcemia-predictive factors after parathyroid surgery, no significant correlation was found between preoperative calcium level and postoperative early hypocalcemia.^[7,19,21,22] In contrast to our study, Brasier et al.^[8] found a higher preoperative calcium level in the group diagnosed

with the hungry bone syndrome after parathyroid surgery than in the normocalcemic group.

In the early postoperative period, intravenous calcium replacement was started in patients with hypocalcemia symptoms and those who had a calcium value below 7.5 mg/dl. Following the daily calcium levels, an oral replacement was started to keep the calcium level at >8.5 mg/dl. In our study, the cases of hypocalcemia extending to the fourth day were calcium and β 8.5 mg/dl cases with oral or intravenous calcium replacement. In literature, the hungry bone syndrome is seen in 12% of the environment after PHPT surgery.^[8,11,20] In our study, total postoperative fourth-day hypocalcemia due to the hungry bone syndrome and transient hypoparathyroidism was 23.3%.

In the study performed by Kaya et al.,^[11] blood urea nitrogen, parathormone and alkaline phosphatase levels were found to be significantly higher in the preoperative period in the group with the hungry bone syndrome, but the volume of adenoma was not evaluated. In the study performed by Jakubauskas et al, the operation time, parathyroid adenoma weight and preoperative parathyroid hormone value were significantly higher in the group with the hungry bone syndrome. For parathormone, the cut-off value is 45 pmol/l.^[23]

Similarly, in the study performed by Kald et al.,^[22] Parathormone elevation was found to be related to severe hypocalcemia in the preoperative period and cut-off value was accepted as 25 pmol/l. Although there were publications supporting the relationship between low 25-OHD and postoperative hypocalcemia in the preoperative period,^[24] a recent study found no association between pre-operative 25-OHD deficiency and hungry bone syndrome, indicating a high level of preoperative parathormone level as the only significant risk factor.^[25]

In our study, preoperative parathyroid hormone and parathyroid adenoma volume were significantly higher in late hypocalcemia extending to postoperative fourth day, whereas preoperative 25 OHD and preoperative phosphorus were significantly lower. There was no significant relationship between other variables and late hypocalcemia extending to the fourth day. The cut-off value of parathormone was 187.5 pg/ml.

Conclusion

In patients scheduled for parathyroid surgery, the risk of hypocalcemia is higher in the first 24 hours if the calcium value is <12.05 mg/dl in the preoperative period. In patients with parathyroid hormone value > 187.5 pg/ml, parathyroid adenoma volume >1.04 cm³, 25-OHD value <10.5 ng/ml and phosphorus value <2.45 mg/dl, hypocalcemia

may persist longer and may lead to hungry bone syndrome. Particularly important is to determine the factors that will predict postoperative hypocalcemia in the preoperative period in order to protect the patient from the complications due to severe hypocalcemia and to shorten the hospitalization period.

Disclosures

Ethics Committee Approval: The study protocol was approved by The Ethics Committee of Kutahya Dumlupinar University (Date: 08.08.2018, Number: 2018/10-11).

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declared that no conflict of interest.

Authorship Contributions: Concept – F.K.; Design – F.K., M.F.E.; Supervision – F.K., M.F.E.; Materials – F.K., M.F.E.; Data collection and/or processing – F.K., M.F.E.; Analysis and/or interpretation – F.K., M.F.E.; Literature search – F.K.; Writing – F.K., M.F.E.; Critical review – F.K., M.F.E.

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