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Can hypocalcemia occur in the early postoperative period be predict in total thyroidectomy patients? A Prospective Study

Total tiroidektomi hastalarında ameliyat sonrası erken dönemde hipokalsemi gelişebilir mi? Prospektif bir çalışma

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ABSTRACT

One of the most important complications following total thyroidectomy is hypocalcemia. Although 1 to 2% of these are permanent, the rate of temporary hypocalcemia is quite high. In various studies this rate is reported as 10-40%. Therefore, prevention and early diagnosis of hypocalcemia is important. Serum phosphate responds rapidly to changes in circulating PTH levels, and its measurement is readily available in all hospitals. The aim of this study is to compare the value of phosphate measures, which may predict the development of hypocalcemia in the early post operative period following total thyroidectomy, to iPTH and Ca measurements.

In this prospective study, patients who underwent total thyroidectomy in our clinic in a one year, independent of diagnosis were included in a consecutive manner. Calcium measurements were made immediately when symptoms of hypocalcemia developed or 24 hours postoperatively in symptom free patients and at day 5 postoperatively to evaluate late hypocalcemia. In our study calcium levels under 8 mg/dl were accepted as hypocalcemia and iPTH levels less than 10 pg/dl were accepted as below normal levels.

120 patients who underwent total thyroidectomy in our clinic were included in this study. The hypocalcemic group included 4 patients with hypocalcemia occurring in the first 24 hours post op, 31 patients at 24 hours and 9 cases were hypocalcemia occurred 5 days postop after the patients had normal calcium and were discharged from the hospital. The normocalcemia group had 76 patients (63,33).

Temporary hypocalcemia occurs in 10% to 40% of patients after total thyroidectomy. The main accepted reason of this situation that occurs following thyroidectomy is parathyroid insufficiency. Even though one of the important goals in modern thyroid surgery is protecting the functions of the parathyroid glands, hypocalcemia following thyroidectoy remains a problem. For this reason, detecting patients that may become hypocalcemic in the postoperative early phase and preventing its occurrence with appropriate treatment will decrease the post operative duration of hospitalization. This being the case, it has made us think that phosphate may be a usable measure to detect post thyroidectomy hypocalcemia earlier.

In light of our findings, we suggest that phosphate levels measured in the early postoperative phase of total thyroidectomy, can be used to predict the development of hypocalcemia.

Keywords: Hypocalcemia; thyroidectomy; phosphate

ÖZET

Total tiroidektomi sonrası en önemli komplikasyonlardan biri hipokalsemidir. Bunların %1-2'si kalıcı olmasına rağmen geçici hipokalsemi oranı oldukça yüksektir. Çeşitli çalışmalarda bu oran %10-40 olarak bildirilmektedir. Bu nedenle hipokalseminin önlenmesi ve erken tanısı önemlidir. Serum fosfat, dolaşımdaki PTH seviyelerindeki değişikliklere hızla yanıt verir ve ölçümü tüm hastanelerde kolaylıkla yapılabilir. Bu çalışmanın amacı total tiroidektomi sonrası erken postoperatif dönemde hipokalsemi gelişimini öngörebilecek fosfat ölçümlerinin değerini iPTH ve Ca ölçümleriyle karşılaştırmaktır.

Bu prospektif çalışmaya kliniğimizde bir yıl içinde total tiroidektomi yapılan, tanıdan bağımsız hastalar ardışık olarak dahil edildi. Kalsiyum ölçümleri hipokalsemi semptomları geliştiğinde hemen veya semptomsuz hastalarda postoperatif 24 saat sonra, geç hipokalsemiyi değerlendirmek için postoperatif 5. günde yapıldı. Çalışmamızda kalsiyumun 8 mg/dl'nin altında olması hipokalsemi, iPTH'nin 10 pg/dl'nin altında olması ise normalin altında olarak kabul edildi.

Bu çalışmaya kliniğimizde total tiroidektomi yapılan 120 hasta dahil edildi. Hipokalsemik grup, ameliyat sonrası ilk 24 saatte hipokalsemi gelişen 4 hastayı, 24 saatte 31 hastayı ve ameliyattan 5 gün sonra normal kalsiyuma ulaşıp hastaneden taburcu olduktan sonra hipokalsemi gelişen 9 hastayı içeriyordu. Normokalsemi grubunda 76 hasta vardı (63,33).

Total tiroidektomi sonrası hastaların %10 ila %40'ında geçici hipokalsemi ortaya çıkar. Tiroidektomi sonrası ortaya çıkan bu durumun kabul edilen temel nedeni paratiroid yetmezliğidir. Modern tiroid cerrahisinde önemli hedeflerden biri paratiroid bezlerinin fonksiyonlarını korumak olsa da tiroidektomi sonrası hipokalsemi sorun olmaya devam etmektedir. Bu nedenle postoperatif erken dönemde hipokalsemik hale gelebilecek hastaların tespit edilmesi ve uygun tedavi ile ortaya çıkmasının önlenmesi, ameliyat sonrası hastanede kalış süresini azaltacaktır. Durum böyle olunca fosfatın tiroidektomi sonrası hipokalsemiyi erken tespit etmede kullanılabilir bir ölçüm olabileceğini düşündürdü.

Bulgularımız ışığında, total tiroidektominin ameliyat sonrası erken döneminde ölçülen fosfat düzeylerinin hipokalsemi gelişimini öngörmede kullanılabileceğini düşünüyoruz.

Anahtar kelimeler: Hipokalsemi; tiroidektomi; fosfat

INTRODUCTION

One of the most important complications following total thyroidectomy is hypocalcemia. Although 1 to 2% of these are permanent, the rate of temporary hypocalcemia is quite high. In various studies this rate is reported as 10-40%. Therefore, prevention and early diagnosis of hypocalcemia is important. There has been no scannig vay for diagnosing. Serum calcium and parathyroid hormone (PTH) measurements are currently used to predict hypocalcaemia after thyroidectomy (1,2). The rate of calcium drop after thyroidectomy is important, not only the values themselves (3). A retrospective study showed that a decrease of 1 mg/dL calcium over 12 hours after surgery is independently correlated with the risk of symptomatic hypocalcemia (3). Other authors found that PTH at one hour after thyroid resection during a partial/subtotal thyroidectomy procedure has a predictive power of 94.4% (4). Moreover, a combination of PTH and calcium assay might be more accurate to indicate the need for calcium replacement (4). Low levels of pre-operatory calcium, 25-hydrroxivitamin D and PTH also might be predictive for their post-operatory values (4). Also, high prevalence in general population of vitamin D deficiency which is an independent contributor to hypocalcemia following thyroidectomy (5).

Serum phosphate responds rapidly to changes in circulating PTH levels, and its measurement is readily available in all hospitals. İn literature, there is one article about serum phosphate assay following thyroidectomy and stated that it is a reliable biochemical predictor of post-thyroidectomy hypocalcaemia (6). However, there is still matter of debate which is the exact test to predict hypocalcemia and exact timing of post-operatory assay.

The aim of this study is to compare the value of phosphate measures, which may predict the development of hypocalcemia in the early post operative period following total thyroidectomy, to iPTH and Ca measurements.

MATERIAL and METHOD

In this prospective study, 120 patients who underwent total thyroidectomy, regardless of diagnosis, between July 2021 and July 2022 in our clinic were consecutively included. In our study, exclusion criteria was the presence of preexisting or diagnosed disorders that can affect calcium metabolism such as Parathyroid diseases, Vitamin D deficiency, Medullary thyroid cancer, chronic renal failure and hypoalbuminemia. Adult patients over the age of 18 were included in our study. Venous blood samples for Calcium (Ca+2), Phosphate (PO4-3) and iPTH measurements were taken from the study patients approximately 24 hours before surgery and shortly after the patient was brought back to their beds on the surgery ward. Calcium measurements were made immediately when symptoms of hypocalcemia developed or 24 hours postoperatively in symptom free patients and at day 5 postoperatively to evaluate late hypocalcemia. In our study calcium levels under 8

mg/dl were accepted as hypocalcemia and iPTH levels less than 10 pg/dl were accepted as below normal levels.

All surgical procedures were performed by one specialist thyroid surgeon or were supervised by him. During the operations, parathyroid glands were identified with careful dissection and protected. Additionally, the recurrent laryngeal nerves were carefully identifed and protected. There was no parathyroid tissue detected in any of the pathology samples retrieved from patients in this study. The patients were divided into two groups, ones that developed hypocalcemia and ones that did not. Demographic data including age, gender, pre-operative laboratory data, postoperatively measured early iPTH, phosphate and calcium levels of these groups were compared.

Statistics

The SPSS for Windows version 17.0 (SPSS, Inc, Chicago, Illinois) program was used for statistical analysis in our study. Results were expressed as mean and standard deviation. The Student's t test, X2 test and Fisher's exact test were used for univariate comparisons and logistic regression analysis was used for multivariate analyses in comparing the two groups. If the P value was measured less than 0.05 (2-tailed), the difference between groups was accepted as significant.

RESULTS

Patients

120 patients who underwent total thyroidectomy in our clinic were included in this study. The hypocalcemic group included 4 patients with hypocalcemia occurring in the first 24 hours post op, 31 patients at 24 hours and 9 cases were hypocalcemia occurred 5 days postop after the patients had normal calcium and were discharged from the hospital. The normocalcemia group had 76 patients (63.3%).

Demographic and Preoperative Data

There was no statistically significant difference found in the comparison of demographic data of the two groups (Table 1). No significant difference was detected between the two groups with regard to preoperative laboratory data (Table 2).

Table 1: Demographic data.

	Hipocalcemia	Normocalcemia	*p*
Age	49,66±12,24	50,74±11,13	*0,62*
Gender (F/M)	36/8	58/18	*0,48*

Table 2: Preoperative Ca++ levels.

	Ca status	N	Mean	*p*
iPTH	Hipocalcemia	44	56,11±37,11	*0,15*
	Normocalcemia	76	67,44±43,87	
Calcium	Hipocalcemia	44	9,33±0,52	*0,17*
	Normocalcemia	76	9,45±0,48	
Phosphate	Hipocalcemia	44	3,38±0,56	*0,28*
	Normocalcemia	76	3,28±0,45	
Creatinin	Hipocalcemia	44	0,63±0,14	*0,69*
	Normocalcemia	76	0,65±0,17	
Albumin	Hipocalcemia	44	4,11±0,29	*0,11*
	Normocalcemia	76	4,19±0,24	

Postoperative Data

iPTH

The average iPTH levels in the postoperatively early phase were found to be significantly lower in the hypocalcemia group than the normocalcemia group both in univariate and multivariate statistical analyses (32,67±28,21 pg/ml vs. 49,06±27,26 pg/ml , p=0,002) (Table 3). Also, a iPTH value of less than 10 pg/ml was found level to be occurring significantly more often in the hypocalcaemia group than the normocalcemia group both in univariate and multivariate analysis (%29,55 vs. %7,89, p=0,002). Another variable evaluated in our study was the number of patients that had a 50% or more decrease in postoperative iPTH as compared to their preoperative levels. Even though the rate of patients in the hypocalcemia group who had 50% and more decrease in iPTH levels was significantly higher than the normocalcemia group in univariate analysis, the independency of this variable could not be confirmed in multivariate analysis.

Calcium

The average calcium value in the post operative early phase was found to be significantly

lower in the hypocalcaemia group than the normocalcemia group both in univariate and multivariate analysis (8,45±0,53 vs. 8,93±0,63, p < 0,001) (Table 3). The ratio of patients that had Calcium values less than 8 mg/dl were found to be significantly higher in the hypocalcaemia group than the normocalcemia group both in univariate and multivariate analysis (%18,18 vs. %5,26 , p=0,022).

Phosphate

Average PO4-3 levels in the postoperative early phase were found to be significantly higher in the hypocalcaemia group than in the normocalcemia group both in univariate and multivariate analysis (Table 3). Also the ratio of patients that had PO4-3 levels over 3,5 mg/dl were found to be significantly higher in the hypocalcemia group than the normocalcemia group both in univariate and multivariate analysis.

Combined Evaluations

In combined evaluations, where the threshold values of 3 measured parameters are taken into account, it was found that postoperative hypocalcemia develops in patients if any two parameters are positive (100%) (Table 5).

Specificity Sensitivity Analysis

Another variable evaluated in our study is the sensitivity and specificity of these parameters alone or combined for predicting postoperative hypocalcemia (Table 6). Values of PO4-3 over 3,5 mg/dl was found to be the most sensitive parameter in predicting postoperative hypocalcemia with a rate of 59.09% The specificity of this parameter was found to be 67, 1%. The sensitivity and specificity of a measured iPTH value below 10 pg/ml was 29,55% and 92,11% respectively. The sensitivity and specificity of a measured value less than Ca levels 8 mg/dl was 18,18% and 94,74% respectively (Table 6).

DISCUSSION

Temporary hypocalcemia occurs in 10% to 40% of patients after total thyroidectomy (7,8). The main accepted reason of this situation that occurs following thyroidectomy is parathyroid insufficiency (1). Even though one of the important goals in modern thyroid surgery is protecting the functions of the parathyroid glands, hypocalcemia following thyroidectoy remains a problem (2,9). Even if the parathyroids are protected during surgery, they can be devascularised by manipulations or can be exposed to temporary ischemia from venous engorgement.

Hypoparathyroidism following thyroidectomy was first described by Weiss in 1883 (10). However the cause-pathogenesis relationship was first described by Eiselberg, a student of Billroth. Even though hypocalcemia can occur in the first 24 hours, it commonly occurs at the end of the first 48 hours and can extent up to 6 months to a year. If it does not improve at the end of this period, we can refer to it as permanent hypoparathyroidism (11). Fortunately, this situation is very rare.

Table 3: Postoperative univariate and multivariate analysis-1.

	Ca^{++} status	N	Mean	Median (Range)	*p*	Logistic regression analysis	
						OR (95% CI)	*p*
Phosphate (mg/dl)	Hipocalcemia	44	3,58±0,49	3,5 (2,5-4,6)	*0,002*	6,61 (2,33-18,71)	*< 0,001*
	Normocalcemia	76	3,25±0,56	3,2(2,0-4,8)			
iPTH (pg/ml)	Hipocalcemia	44	32,67±28,21	29 (1,4-111)	*0,002*	0,98 (0,96-0,99)	*0,005*
	Normocalcemia	76	49,06±27,26	45 (2,4-129)			
Calcium (mg/dl)	Hipocalcemia	44	8,45±0,53	8,4 (7,4-11)	*< 0,001*	0,11 (0,04-0,31)	*< 0,001*
	Normocalcemia	76	8,93±0,63	8,8 (7,6-11)			

Table 4: Postoperative univariate and multivariate analysis-2.

	Ca^{++} status	N (%)	*p*	Logistic regression analysis	
				OR (95% CI)	*p*
Phosphate ≥ 3,5 mg/dl	Hipocalcemia	26 (59,09)	*0,005*	0,30 (0,13-0,69)	*0,005*
	Normocalcemia	25 (32,89)			
IPTH < 10 pg/ml	Hipocalcemia	13 (29,55)	*0,002*	0,22(0,06-0,80)	*0,022*
	Normocalcemia	6 (7,89)			
Calcium ≤ 8 mg/dl	Hipocalcemia	8 (18,18)	*0,023*	0,14(0,03-0,66)	*0,012*
	Normocalcemia	4(5,26)			
	Hipocalcemia	16(36,36)			

iPTH Decrease more than %50	Normocalcemia	14(18,42)	*0,029*	0,60 (0,21-1,71)	*0,344*

Table 5: Combined evaluation.

	N	Hipocalcemia (%)	Normocalcemia (%)	*p*
iPTH < 10 pg/ml + Phosphate ≥ 3,5 mg/dl	10	10 (100)	0(0)	*< 0,001*
iPTH < 10 pg/ml + Calcium ≤ 8 mg/dl	4	4(100)	0(0)	*0,017*
Phosphate ≥ 3,5 mg/dl + Calcium ≤ 8 mg/dl	6	6(100)	0(0)	*0,002*
iPTH < 10 pg/ml + Calcium ≤ 8 mg/dl + Phosphate ≥ 3,5 mg/dl	3	3(100)	0(0)	*0,047*

Table 6: Specificity sensitivity analysis.

	Sensitivity (95% CI)	Specifity (95%CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Phosphate ≥ 3,5 mg/dl	59,09	67,10	50,98	73.91
iPTH < 10 pg/ml	29,55	92,11	68,42	69,31
Calcium ≤ 8 mg/dl	18,18	94,74	66,67	66,67
iPTH ≤ 10 pg/ml + Phosphate ≥ 3,5 mg/dl	22,73	100	100	69,09
iPTH < 10 pg + Calcium ≤ 8 mg/dl	9,09	100	100	65,52
Phosphate ≥ 3,5 mg/dl + Calcium ≤ 8 mg/dl	13,64	100	100	66,67
iPTH < 10 pg/ml+ Calcium≤ 8 mg/dl + Phosphate ≥ 3,5 mg/dl	6,82	100	100	64,96

Patients are generally observed for bleeding that can occur in the first 24 hours following thyroidectomy and discharged at the end of 24 hours. The most important factor that prolongs hospitalization after thyroidectomy is postoperative hypocalcemia. For this reason, detecting patients that may become hypocalcemic in the postoperative early phase and preventing its occurrence with appropriate treatment will decrease the post operative duration of hospitalization. Thus, patient satisfaction will increase and hospital costs will be reduced. The most common parameter used in studies conducted for this purpose is the measurement of serum PTH levels (1,12-18). In the study by Grodski et al. it was demonstrated that the measurement of serum PTH can reduce the duration of hospitalization following thyroidectomy. However, measurement of PTH is relatively expensive and is not possible to measure in many hospitals even in western countries. Also there is no clear consensus on the matter of post thyroidectomy PTH measurement time and threshold for starting treatment. In the study by Toniato et al. conducted with 160 patients, even the measurement of PTH on the first postoperative day was found to be an usable method to predict hypocalcemia development (18). In a meta analysis by Noordzij et al that included 457 patients from 9 studies, they reported that the PTH value 1 to 6 hours postoperatively was found to have a higher accuracy than values measured in the first 20 minutes and after 6 hours (19). For this reason, we preferred to measure the PTH levels as the patients left the operating room and were taken to the surgery ward, in other words approximately one hour postoperatively.

Phosphate is an inorganic chemical and a phosphoric acid salt. It generally exist as organophosphate (phosphoric acid ester) in organic structures. Approximately 12 grams of phosphate exists per kilogram in the human body. As only1.4 gr/kg is found in soft tissues, the rest is found in bones in mineralized form. In adults, the normal density of serum phosphate is 2.8-4.5 mg/dl. The most important organ for phosphate balance is kidney. In phosphate metabolism PTH plays the role as the main regulator. PTH increases phosphate excretion by preventing phosphate re-absorption both in the proximal and distal renal tubules. In many conducted animal and clinical studies, it has been noted that serum phosphate is affected quickly by changes in PTH (20, 21). In humans it has been demonstrated that phosphate

gives an earlier response than calcium to changes in PTH levels (21-25). This being the case, it has made us think that phosphate may be a usable measure to detect post thyroidectomy hypocalcemia earlier.

From what we know, our study is the second study that evaluates the measurement of phosphate in predicting the development of postoperative hypocalcaemia. In a retrospective study on this subject, of Sam et al with 112 cases, they concluded that in patients with normal vitamin D levels early phase phosphate elevation is valuable in predicting postoperative hypocalcemia. When the results of our study are evaluated, the 3 parameters measured at the early postoperative phase (iPTH, Ca,P) demonstrated no significant statistical difference between the hypocalcemic and normocalcemic groups. Thus, the average PTH and calcium values in the hypocalcemic group were lower than in the normocalcemic group, whereas average phosphate levels were high. Moreover, the percentage of patients with a PTH level lower than the accepted borderline value of 10pg/ml were significantly higher in the hypocalcemic group than the normocalcemic group statistically. Similarly the percentage of the patients with a Calcium level under 8 mg/dL was found to be significantly higher in the hypocalcemic group than the normocalcemic group statistically. If we accept the medium value of phosphate measured in patients that developed hypocalcemia as 3.5 mg/dL, the percent of patients above 3.5 mg/dL in the hypocalcemic group was found to be significantly higher than in the normocalcemic group. Another evaluation made in our study was the sensitivity and specificity of these parameters in predicting hypocalcaemia. It has been demonstrated that, among the measured parameters (iPTH, Ca,P), the measurement of PO4-3 above 3,5 mg/dl was the most sensitive (59,09%) parameter in predicting postoperative hypocalcemia. The specificity of this parameter was 67.1%. In our study, the highest specificity of predicting postoperative hypocalcemia was found to be measurement of postoperative early phase calcium levels under 8mg/dL. It has been demonstrated that PTH levels under 10pg/mL has a specificity close to that of calcium measurements. However the sensitivities of these two parameters were found to be rather lower than phosphate measurements. Another remarkable result of our study is in the combined evaluations of taking the threshold levels of these three parameters, where patients with any two positive parameters developed postoperative hypocalcemia (100%). This situation in combined evaluations means 100% specificity and 100% positive predictability.

Conclusion

In light of our findings, we suggest that phosphate levels measured in the early postoperative phase of total thyroidectomy, can be used to predict the development of hypocalcemia. Phosphate measurement can be used as an alternative particularly in centers where iPTH measurement cannot be performed. Another important finding in our study that should be emphasized is the full accuracy with which combining these parameters can predict a patients hypocalcemia development. We suggest that calcium treatment may be initiated in the postoperative early phase to patients who have two positive parameters as a result of combined measurements.

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