






# The effect of different therapeutic treatments on the frequency of postoperative hypocalcemia in patients with thyroidectomy

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## ABSTRACT

**Objective:** Thyroid gland surgery and its surgical complications are situations that a surgeon frequently encounters in his daily practice. In our study, it was aimed to examine the effect of different treatment methods given to patients who underwent thyroidectomy on hypocalcemia.

**Material and Methods:** Three hundred and seventy-one patients who underwent thyroidectomy at Ondokuz Mayıs University Medical Faculty General Surgery clinic between December 2016 and January 2021 were retrospectively included in the study. Parameters such as surgery indications, fine needle aspiration biopsy results, preoperative serum calcium values, type of surgery, serum calcium values at postoperative 1<sup>st</sup> day and 1<sup>st</sup> month, postoperative hospital stay, drugs prescribed at discharge, histopathological diagnosis of the patient, and whether there was incidental parathyroidectomy or not were included.

**Results:** Mean age of 371 patients who underwent thyroidectomy was 49 (19-82) years. Total thyroidectomy was the most common type of thyroidectomy with 61% (n= 225) of the patients. There was a significant decrease in pre-op and post-op calcium values in all three types of surgery performed on the patients, and there was no significant difference between the different types of surgery. Post-operative day one and month one serum calcium values were significantly increased in all groups (p= .000). The increase in post-op serum calcium level was most common in the group using calcium carbonate + cholecalciferol + calcitriol.

**Conclusion:** The use of post-op calcitriol in patients undergoing thyroidectomy seems to be quite effective in preventing the development of hypocalcemia.

**Keywords:** Thyroidectomy, hypocalcemia, calcitriol, thyroid diseases

## INTRODUCTION

Thyroid gland diseases are conditions affecting approximately 5% of the population and are frequently encountered by a surgeon in his/her daily practice (1). Although thyroid surgery is considered a low-risk and safe approach today, the patient should be followed closely for postoperative complications (2).

The first successful thyroid surgery in humans was performed and documented by Ebu'l Kasım El Zehravi (963-1013) (3). It is also called Albucasis or Elzahawi in European sources. These methods were published by Roger Frugardi in 1170 (4). Thyroid surgery, which had a mortality rate of approximately 40% until the 1850s, became much less mortal and effective especially after the 1850s (5).

However, another problem is hypothyroidism, which develops in patients who survive thyroidectomy. This condition was first treated with subcutaneous injection of the thyroid extract in 1891, and after the effectiveness of the treatment was proven, it was discovered that oral therapy had similar efficacy, and oral replacement therapy was started (6).

Today, oral replacement therapy is not only for hypothyroidism, but also for calcium deficiencies (7,8). Postoperative hypocalcaemia can be affected by many conditions such as the surgeon, the center, and the risk factors of the patient, and it can be seen in the literature at rates up to 50% (2,8,9). Postoperative hypocalcaemia may be asymptomatic or may be of varying severity ranging from tetany,

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laryngospasm, cardiac arrhythmias and death (10). Therefore, surgeons should diagnose and treat postoperative hypocalcaemia in a timely manner. On the other hand, preoperative and postoperative calcium and vitamin D preparations are recommended in the American Thyroid Association guidelines although there is no consensus on a standard prevention treatment (10). In our study, it was aimed to examine the effect of prophylactic hormone therapy given to patients who underwent thyroidectomy on hypocalcaemia.

## MATERIAL and METHODS

The study retrospectively included 371 patients who underwent bilateral total thyroidectomy, completion thyroidectomy, and intrathoracic substernal thyroidectomy by the same surgeon in the General Surgery clinic of Ondokuz Mayıs University Faculty of Medicine between December 2016 and January 2021.

Parameters such as patients' indications for surgery, fine needle aspiration biopsy results, preoperative serum calcium values, type of surgery, serum calcium (n= 8.5-10.3 mg/dL) values at postoperative 1<sup>st</sup> day and 1<sup>st</sup> month, postoperative hospital stay, drugs prescribed at discharge, histopathological diagnosis, and whether there was an incidental parathyroidectomy or not were included in the study.

Patients who had deficiencies in these parameters, did not come to their follow-ups, cases with accompanying parathyroid surgery or those who did not use the prescribed drugs were excluded from the study.

The patients were divided into three groups according to the treatments they received (or did not receive). No drugs, calcium carbonate + cholecalciferol or calcium carbonate + cholecalciferol + calcitriol. Only calcium carbonate + cholecalciferol was started in patients with symptomatic hypocalcaemia. If the patient had symptomatic hypocalcaemia at discharge and parathormone levels were below the normal range, calcitriol was added. The treatment was terminated if parathormone values were found to be normal in the postoperative one-month follow-up.

Since the center where the study was conducted is an education clinic dealing with oncological cases, central lymph node dissection with nerve monitoring is routinely performed in all cases.

IBM SPSS (Statistical Package for the Social Sciences) 20.0 package program was used for data analysis. Descriptive statistics were summarized as frequency and percentage. Chi-square test was used for comparison of qualitative variables, Student-t test, Mann-Whitney U and ANOVA tests were used for comparisons of independent groups. Wilcoxon test was used for dependent group comparisons. However, corrections were not made for multiple comparisons.

Approval for this study was obtained from the Clinical Research Ethics Committee of Ondokuz Mayıs University with the application dated 16.04.2020 and application number 2020000416-5.

Statistical significance level was taken as  $p < .05$ .

## RESULTS

Mean age of 371 patients who underwent thyroidectomy was 49 (19-82) years. Total thyroidectomy was the most common type of total thyroidectomy with 61% (n= 225) of the patients (Table 1).

Incidental parathyroidectomy was seen in 20.1% of the patients (n= 72), and no significant correlation was found between the types of surgery and the incidence of incidental parathyroidectomy ( $p = .453$ ). Hypocalcaemia was observed in 69.4% (n= 50) of 72 patients with incidental parathyroidectomy and 47.4% (n= 136) of 287 patients without incidental parathyroidectomy. Mean serum calcium level of the patients with incidental parathyroidectomy was 8.2 (min= 6.1, max= 9.9) while the mean of patients without incidental parathyroidectomy was 8.5 (min= 5.8, max= 11.5). Presence of incidental parathyroidectomy has a statistically significant effect on hypocalcaemia ( $p = 0.001$ ).

Serum PTH levels were measured on post-op day one from 346 patients. Median value was found to be 24.66 pg/mL (min= 1.2, max= 168.6) (normal value= 15-65 pg/mL). There was a statistically significant difference between the groups with and without incidental parathyroidectomy ( $p < 0.001$ ).

In 71% (n= 262) of the patients, the biopsy result was malignancy or suspected malignancy, and no suspicion of malignancy was found in 29% (n= 109). Of the patients, 88% (n= 325) were hospitalized for less than one postoperative day. Calcium levels observed in the postoperative 1<sup>st</sup> day and 1<sup>st</sup> month controls of the patients are given in Table 2.

Mean post-op calcium values of 325 patients who were discharged one day after the operation were  $8.45 \pm 0.613$ , and the average of 46 patients who were discharged more than two days later was  $7.793 \pm 0.796$ , and the difference between them was statistically significant ( $p < 0.001$ ) (Table 3).

There was a significant decrease in preoperative and postoperative calcium values in all three types of surgery, and no significant difference was observed between the different types of surgery (Table 4).

**Table 1.** Distribution of thyroidectomy types applied to patients

Type of surgery	n	%
Total thyroidectomy	225	61
For completion + recurrence	51	13
Intrathoracic-substernal	95	26
Total	371	100

**Table 2.** Hypocalcaemia development rates of the patients on the postoperative 1<sup>st</sup> day (Post-op-1) and postoperative 1<sup>st</sup> month (Post-op-control)

Followed patient group	n	%
Post-op-1 hypocalcaemia, post-op-control hypocalcaemia	24	6.4
Post-op-1 hypocalcaemia, post-op-control normocalcemia	171	46.1
Post-op-1 normocalcemia, post-op-control hypocalcaemia	4	1.2
Post-op-1 normocalcemia, post-op-control normocalcemia	172	46.3

**Table 3.** Hypocalcaemia development status according to discharge days

Development of hypocalcaemia	Discharge day				p
	Day 1		Day 2 and later		
	n	%	n	%	
No	172	95	9	5	<b>&lt;0.001</b>
Yes	153	80.5	37	19.5	
Total	325	87.6	46	12.4	

**Table 4.** Calcium values before and after the operation according to the types of surgery (mg/dL)

Type of surgery	Pre-op/Post-op	Median	Min	Max	p
Total thyroidectomy	Pre-op	9.5	7.8	11.6	<b>&lt;0.001</b>
	Post-op	8.4	5.8	10.2	
Completion thyroidectomy	Pre-op	9.4	7.5	12	<b>&lt;0.001</b>
	Post-op	8.6	6.4	9.5	
Intrathoracic	Pre-op	9.6	8.1	12.9	<b>&lt;0.001</b>
	Post-op	8.4	6.1	11.5	

In 98% (n= 364) of the patients, levothyroxine 100 microgram was started on the 1<sup>st</sup> postoperative day. Likewise, 2500 mg calcium carbonate + 9.68 mg cholecalciferol was started in 90% (n= 334) of the patients, and calcitriol 0.25 microgram was started in 23% (n= 86) of the patients.

Regardless of the drug effect, there is a time-dependent increase in serum calcium values even if the patients do not use any drugs. The change in serum calcium values over time according to the drug groups used is given in Table 5, and post-

op 1<sup>st</sup> day and 1<sup>st</sup> month serum calcium values increased significantly in all groups (p< 0.001).

Post hoc multiple comparison test was performed to determine the difference between the groups. Accordingly, the difference in post-op 1<sup>st</sup> day and post-op 1<sup>st</sup> month serum calcium levels was significantly higher in the group using calcium carbonate + cholecalciferol + calcitriol compared to the other two groups (p= .004, p= .041, respectively) (Table 6).

**Table 5.** Post-op 1<sup>st</sup> day and post-op 1<sup>st</sup> month serum calcium values according to the drug groups used (mg/dL)

Group	n	Post-op 1 <sup>st</sup> day average	Post-op 1 <sup>st</sup> month average	Difference (mean ± Std. deviation)	p
No drugs	25	9	9.6	0.652 ± 0.142	<b>&lt;0.001</b>
Calcium carbonate + cholecalciferol	212	8.5	9.5	0.956 ± 0.42	<b>&lt;0.001</b>
Calcium carbonate + cholecalciferol + calcitriol	78	7.8	9.05	1.275 ± 0.12	<b>&lt;0.001</b>

\*Patients with missing data were not included.

**Table 6.** Multiple comparison results of post-op 1<sup>st</sup> day and post-op 1<sup>st</sup> month serum calcium levels difference according to the drug use groups (mg/dL)

Drug		Mean difference	Standard error	p
No drugs	Calcium carbonate + cholecalciferol	-0.30	.15	.141
	Calcium carbonate + cholecalciferol + calcitriol	-0.62	.19	<b>.004</b>
Calcium carbonate + cholecalciferol	No drugs	0.30	.15	.141
	Calcium carbonate + cholecalciferol + calcitriol	-0.32	.13	<b>.041</b>
Calcium carbonate + cholecalciferol + calcitriol	No drugs	0.62	.19	<b>.004</b>
	Calcium carbonate + cholecalciferol	0.32	.13	<b>.041</b>

## DISCUSSION

Thyroid pathologies are one of the most common endocrine pathologies after diabetes mellitus, and therefore, thyroid operations are very vital in the general surgical practice (11). Postoperative hypocalcemia after thyroidectomy is one of the most common complications, and it has been reported in the literature that temporary hypocalcemia can occur at a rate of 6-50% and permanent hypocalcemia at a rate of 1-2% (2,9,12,13). In our study, it was aimed to evaluate the efficacy of drug treatments for hypocalcemia in 371 patients operated in our center.

In patients with positive malignancy, the rate of bilateral total thyroidectomy and complementary thyroidectomy surgery increases, on the contrary, the rate of intrathoracic-substernal thyroidectomy decreases (14,15). In our study, 71% (n= 262) of the patients had biopsy results as malignancy or suspected malignancy, therefore, the rates of total thyroidectomy were higher than intrathoracic-substernal thyroidectomy.

Due to its anatomical variations, even with careful dissection and sufficient anatomical information, it is very difficult to recognize and preserve the parathyroid tissue during the operation. In the literature, it has been reported that incidental parathyroidectomy occurs in 6-28% of thyroidectomy operations (16). Similarly, incidental parathyroidectomy was found in 20.1% of the patients in our study. In addition, it was observed that the surgical method applied did not make a statistically significant difference in the incidence of incidental parathyroidectomy in the pathology specimen.

Various strategies have been used to diagnose and manage hypocalcaemia after thyroidectomy. The traditional approach to inpatient clinical assessment and monitoring of serum calcium levels is still used by many institutions around the world (17). When the literature is reviewed, many studies have shown that the measurement of serum PTH levels after surgery can be used as a predictor of the development of hypocalcaemia after

thyroidectomy (17-19). Although there are studies suggesting PTH measurement routinely post-op, this approach is not cost-effective. However, since our clinic is an education clinic, serum PTH levels were measured in 93.2% (n= 346) of the patients, and most of them were found to be within the normal range (median= 24.66 pg/mL) (min= 1.2, max= 168.6).

Mean serum calcium (mean= 7.793 ± 0.796) in patients with a hospital stay of two days or longer was found to be lower than the mean calcium (mean= 8.45 ± 0.613) of patients discharged on the 1<sup>st</sup> postoperative day. In this respect, it has been observed that low calcium levels on the first postoperative day are a significant indicator for prolonged hospitalization. However, considering the final serum calcium values, hypocalcemia was observed in only 1.2% (n= 4) of the patients in the post-op 1<sup>st</sup> month controls.

A significant decrease was observed in the mean of pre-op and post-op serum calcium values after thyroidectomy in all age groups, regardless of the type of surgery. The main factor affecting serum calcium values in post-op 1<sup>st</sup> month controls was the type of drug used.

When the postoperative 1<sup>st</sup> month control calcium values were examined, an increase in serum calcium levels was observed even if the patients did not use any medication. Although the lowest increase was observed in this group, the difference in calcium levels between the post-op 1<sup>st</sup> day and 1<sup>st</sup> month was still statistically significant. The highest increase was in the group using calcium carbonate + cholecalciferol + calcitriol.

On the other hand, the difference in calcium levels between the 1<sup>st</sup> day and 1<sup>st</sup> month was not statistically significant between the group that did not use drugs and the group that used only calcium carbonate + cholecalciferol. In a meta-analysis involving 2.285 patients in 2013, it was stated that the use of post-op vitamin D preparations had an effective role in preventing post-op hypocalcemia and its use was recommended (20). In another

study involving 200 patients, the use of vitamin D has been found to be effective in preventing post-op hypocalcemia (21). Similarly, in our study, the increase in serum calcium levels in the group receiving calcitriol + calcium carbonate + cholecalciferol was significantly higher than in both groups.

Our study has some strengths and weaknesses. First, since the patient group followed up with calcitriol in isolation in our clinic is not crowded, the therapeutic and efficacy of calcitriol was demonstrated by comparing three patient groups who did not receive replacement, only calcium carbonate + cholecalciferol, and took both drugs. On the other hand, although Graves' disease is a risk factor for postoperative hypocalcemia, there is no relevant data in our study and we do not have preoperative vitamin D levels of patients for whom we planned total thyroidectomy. In addition, it may be more appropriate to include not only the 1<sup>st</sup> month but also the future follow-ups of the patients. However, after this period, patients either do not come for follow-ups or continue their follow-ups in internal clinics. On the other hand, the selection of patients operated by the same surgeon is one of the strengths of our study in order to include and standardize all patients within a period of more than four years. In addition, the large number of patients included is also statistically significant. However, there is a need for further studies that include patients followed up with calcitriol in isolation and include long-term follow-up results.

## CONCLUSION

In our study, we found that incidental parathyroidectomy was independent of the type of surgery. In the early postoperative period, serum PTH levels of most patients were found to be within the normal range. However, the use of calcitriol appears to be quite effective in patients with decreased PTH levels. On the other hand, even if no post-operative medication was given to the patients, it was observed that the serum calcium levels of the patients increased, which was statistically similar to the group using calcium carbonate + cholecalciferol. The highest increase was in the group using carbonate + cholecalciferol + calcitriol, which was found to be significantly higher than the other groups. The use of post-op calcitriol in patients undergoing thyroidectomy seems to be quite effective in preventing the development of hypocalcemia.

**Ethics Committee Approval:** This study was approved by Ondokuz Mayıs University Clinical Research Ethics Committee (Decision no: OMÜ KAEK 2020/416, Date: 27.08.2020).

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**Conflict of Interest:** The authors have no conflicts of interest to declare.

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### ORJİNAL ÇALIŞMA-ÖZET

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## Tiroidektomi olan hastalarda farklı terapötik tedavilerin postoperatif hipokalsemi sıklığına etkisi

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### ÖZET

**Giriş ve Amaç:** Tiroid bezi cerrahisi ve cerrahi komplikasyonları cerrahın günlük pratiğinde sıklıkla karşılaştığı durumlardır. Çalışmamızda tiroidektomi yapılan hastalara verilen farklı tedavi yöntemlerinin hipokalsemiye etkisinin incelenmesi amaçlanmıştır.

**Gereç ve Yöntem:** Çalışmaya Aralık 2016- Ocak 2021 yılları arasında Ondokuz Mayıs Üniversitesi Tıp Fakültesi Genel Cerrahi kliniğinde tiroidektomi uygulanan 371 hasta retrospektif olarak dahil edildi. Hastaların ameliyat endikasyonları, ince iğne aspirasyon biyopsisi sonuçları, preoperatif serum kalsiyum değerleri, ameliyat tipi, postoperatif birinci gün ve birinci ay serum kalsiyum değerleri, postoperatif yatış süresi, taburculukta reçete edilen ilaçlar, hastanın histopatolojik tanısı, insidental paratiroidektomi olup olmadığı gibi parametreler çalışmaya dahil edildi.

**Bulgular:** Tiroidektomi yapılan 371 hastanın ortalama yaşı 49 (19-82) yıl idi. Hastalara %61 (n= 225) ile en çok total tiroidektomi uygulanmıştı. Hastalara uygulanan üç ameliyat tipinde de pre-op ve post-op kalsiyum değerlerinde anlamlı düşüş mevcut olup farklı ameliyat tipleri arasında belirgin fark görülmemiştir. Tüm gruplarda post-op birinci gün ve birinci ay serum kalsiyum değerleri anlamlı derecede yükselmiştir (p= ,000). Post-op serum kalsiyum düzeyi artışı en çok kalsiyum karbonat + kolekalsiferol + kalsitriol kullanan grupta olmuştur.

**Sonuç:** Tiroidektomi uygulanan hastalarda post-op kalsitriol kullanımı hipokalsemi gelişimini önlemede oldukça etkili görünmektedir.

**Anahtar Kelimeler:** Tiroidektomi, hipokalsemi, kalsitriol, tiroid hastalıkları

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