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An Undesirable Post-Thyroidectomy Surprise for the Surgeon: Inadvertent Parathyroidectomy

Tiroidektomi Sonrasında Cerrah Açısından Hoş Olmayan Bir Sürpriz: İstemeden Yapılan Paratiroidektomi

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Abstract

Objectives: This study aims to report the incidence of inadvertent parathyroid gland removal during thyroidectomies, as documented by pathology reports, and investigate its association with hypocalcemia.
Materials and Methods: The patients who underwent thyroidectomy at our department between 2009 and 2013 were retrospectively reviewed. The patients who had standard total thyroidectomy were included in the study. Data on patient demographics, surgical reports, experience of surgeons, anatomical localization of excised parathyroid glands (PG) and laboratory results were evaluated. Patients were divided into two groups according to the presence or absence of an excised PG in the histopathology report (group P: presence of PG, and group T: absence of PG).
Results: A total of 343 patients were included to study. Of these, 26 patients were in group P, and 317 in group T. Post-operative hypocalcemia was encountered in 37 patients. Hypocalcemia rates were similar between two groups (p=0.45). Surgical experience was found to decrease the rate of Inadvertent parathyroidectomy (IP) (p=0.04), however, it wasn't associated with post-operative hypocalcemia (p=0.72).
Conclusion: IP is an undesirable finding that can be encountered by surgeons. Our findings showed that IP was found to be associated with surgical experience. However, these results were not associated with post-operative hypocalcemia.
Key Words: Inadvertent Parathyroidectomy, Thyroidectomy, Hypocalcemia, İntraoperative Complication

Öz

Amaç: Bu çalışmada tiroidektomi sırasında istenmeden çıkartılan ve patoloji raporlarında saptanan paratiroid bezlerinin insidansının saptanması ve hipokalsemi gelişimi ile ilişkisinin belirlenmesi amaçlanmıştır.
Gereç ve Yöntem: Kliniğimizde 2009 ile 2013 yılları arasında tiroidektomi uygulanan hastalar retrospektif olarak değerlendirildi. Standart total tiroidektomi yapılan olgular çalışmaya dahil edildi. Hastalara ait demografik veriler, ameliyat raporları, cerrahların deneyimi, eksize edilen paratiroid bezinin (PB) anatomik lokalizasyonu ve laboratuvar sonuçları değerlendirildi. Hastalar histopatoloji raporunda paratiroid bezi saptanan ve saptanmayanlar olmak üzere iki gruba ayrıldı. (grup P: PB saptananlar, and group T: PB saptanmayanlar).
Bulgular: Çalışmaya toplam 343 hasta dahil edildi. Bunlar içerisinden, 26 hasta grup P'de, 317'si ise grup T'de yer aldı. Otuz yedi hastada postoperatif dönemde hipokalsemi saptandı. Hipokalsemi oranları her iki grupta benzerdi (p=0,45). Cerrahi deneyimin istemeden yapılan paratiroidektomi (İP) oranını düşürdüğü görüldü (p=0,04), ancak postoperatif hipokalsemi ile ilişkisi saptanmadı (p=0,72).

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Sonuç: İstemeden yapılan paratiroidektomi cerrahlar açısından hoş sonuçlanmayan bir durumdur. Çalışmamıza ait sonuçlar cerrahi tecrübe arttıkça İP oranının azaldığı yönündedir. Ancak bu durum postoperatif hipokalsemi ile ilişkisiz bulunmuştur.
Anahtar Kelimeler: İstemeden Yapılan Paratiroidektomi, Tiroidektomi, Hipokalsemi, İntraoperatif Komplikasyon

Introduction

Accidental removal of the parathyroid gland (PG) is a frequently encountered complication after thyroidectomies and may result in iatrogenic hypocalcemia, which is a well-known major complication following thyroidectomy (1). The mechanism of transient hypocalcemia is multifactorial and still unclear in most of the cases. Direct trauma to the PGs or their devascularization, hypothermia of the glands, extent of surgery or lack of surgical experience are potential risks for hypocalcemia (2-4). Despite recent surgical advances in thyroid surgery, surgeons are still faced with unexpected pathological results indicating parathyroidectomy even after a meticulous resection of the thyroid gland (5). The common vascular supply shared by both parathyroid and thyroid glands together with their close anatomical association or the intrathyroidal location of the gland may be the cause of inadvertent excision of PGs during thyroidectomy (6).

In spite of the low mortality and morbidity rates recorded by modern thyroid surgeries, the effects of iatrogenic hypocalcemia on patients' quality of life still remain a major medical concern (7,8). Rates of iatrogenic hypocalcemia after thyroidectomies as reported in the literature range between 0.5% and 40% (9-12). A greater percentage of these cases are reported as transient, however, 1.5-4% of the cases are known to cause permanent hypocalcemia (3,13-16). While transient hypocalcemia usually resolves on its own via compensatory mechanisms by the parathyroid gland, permanent hypocalcemia may require lifetime medical treatment.

Increased rates of inadvertent parathyroidectomy (IP) after thyroid surgery have been reported by several studies, however, hypocalcemia or hypocalcemic symptoms weren't described in all patients (17-19). Risk factors for inadvertent parathyroid resection and iatrogenic injuries caused to the PG during neck surgeries include, neck dissections, re-operative thyroid surgeries, total thyroidectomy, hyperthyroidism and lack of surgical experience (3,4,17-19).

This study aims to report the incidence of inadvertent PG removal during standard total thyroidectomy, as documented by pathology reports from our center, and investigate its association with hypocalcemia.

Materials and Methods

All thyroidectomies (lobectomy, subtotal and total) performed at our department between January 2009 and May 2013, were retrospectively reviewed. All procedures were performed in a similar fashion with careful dissection along the thyroid capsule attempting to identify and preserve the PGs with their vascular supply, as well as the recurrent laryngeal nerves as described by Bliss et al. (20). Cases that were performed between 2009 and 2012, were done by surgeons who were board certified in general surgery only, however those procedures performed after 2012, were done by two surgeons with specialized training in the field of endocrine surgery (21). A written informed consent for total thyroidectomy was received from all patients. In all pathology specimens, right lobe was sutured for pathologic orientation routinely. Also, the right and left lobes were sent separately if en-bloc resection could not be performed. The lateralization of removed PG was recorded based on this standardized orientation suture on histopathology examination.

Pathology reports of all the patients were evaluated to identify patients who had accidental removal of their PGs during thyroid surgery (Figure 1). The patients who have at least 6 months follow-up period were included into the study. Patients were divided into two groups according to findings from pathological examination of the excised thyroid gland. (group P: presence of PG, group T: absence of PG).

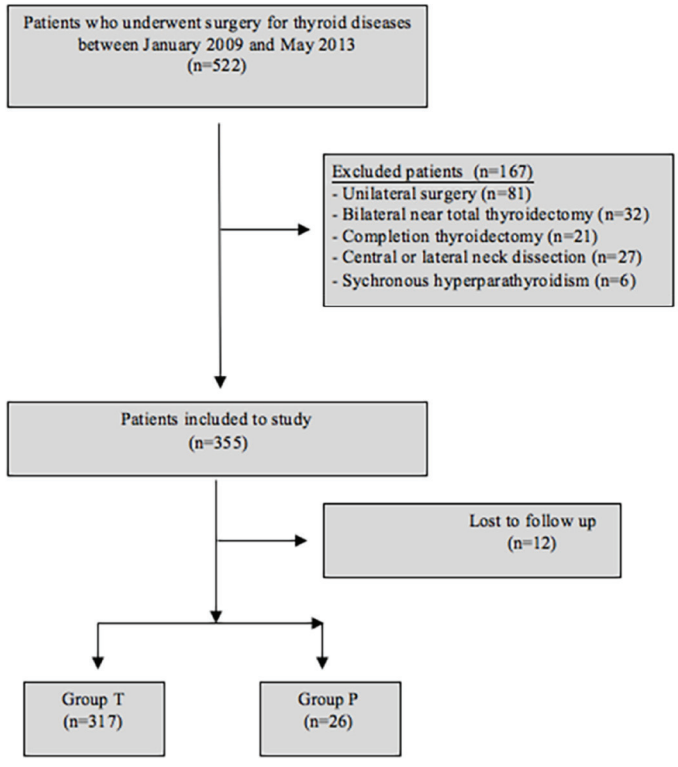

Figure 1: Flow chart of patients included to study

The inclusion criteria for Group P was the presence of PG on the pathological examination of the excised thyroid gland. Therefore, group T includes the cases with absence of PG in the specimen and the cases with parathyroid auto-transplantation. Despite the unclarity on PG's proper function after autotransplatation; the patients with PG autotransplantation were included to group T based on recent studies and the design of the groups in the study (22).

Extent of surgery is one of the described risk factors for IP and/or hypocalcemia in the literature. For the purpose of standardization, patients who (a) underwent other procedures (lobectomy, subtotal thyroidectomy) beside standard total thyroidectomy, (b) had a pre-operative diagnosis of malignancy, (c) were admitted for completion thyroidectomy, (d) were planned for additional procedures (prophylactic or theurapeutic neck dissection) and (e) hyperparathyroid patients in whom additional interventions were planned were excluded from study (Figure 1). Post-operative calcium status were seen at the morning of post operative day (POD) 1 before discharge home, at first week, first month, 3rd month and 6th month of surgery at outpatient clinic visits. Asymptomatic (biochemical) hypocalcemia was defined when serum total calcium level was measured below 8 mg/dL, symptomatic hypocalcemia was defined when there was any clinical signs of hypocalcemia such as tingling and numbness, nerve hyperexcitability (Chvostek's sign) and/or latent tetany (Trousseau's sign) seen during the hospital stay. Permanent hypocalcemia was defined as persistance of hypocalcemia after 6th month of surgery.

Data on patient demographics, pre and post-operative laboratory results, surgical and medical history were obtained. Also, the information from pathology reports, anatomic localization of excised glands, postoperative hypocalcemia symptoms, total serum calcium, parathormone, 25-OH Vit D and albumin levels, postoperative treatment and duration of hospital stay were included in the data collection. These findings were compared between the two groups. Patients in whom postoperative hypocalcemia developed were hospitalized and observed closely until hypocalcemic symptoms resolved and later on discharged with appropriate calcium and vitamin D prescriptions. All other postoperative complications were noted.

Data was anonymously entered into a computerized database program (Excel 2007, Microsoft Inc., Redmond, WA) for individual privacy protection. In terms of anonymized data usage and retrospective manner of the study, no local ethics committee approval was obtained. Therefore, the study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. This manuscript was prepared in accordance with STROBE guidelines for case control studies.

Statistical Analysis

Data was analyzed using a statistical package software (JMP® version 10.0.0, SAS®, Cary, NC). Continuous variables were expressed as mean ± SD and categorical variables as frequencies and percentages. Comparison of continuous variables was performed using the student's t-test. The chi-square tests were used in the comparison of categorical variables and Mann-Whitney U test was used for comparison on non-parametric variables. Univariate and multivariate analysis with nominal regression model were performed to identify factors that predicted postoperative transient and permanent hypocalcemia. P values of 0.05 or less was considered as statistically significant.

Results

Between January 2009 and May 2013, a total of 522 adult patients underwent thyroidectomies (lobectomy, subtotal and total) at our department. Of these, data on 355 patients who met the study criteria was evaluated and 167 patients were excluded from the study. Twelve of these 355 patients have been lost to follow up and the data of remaining 343 patients was completely recorded (Figure 1). The median age was 48 years (20-81) and female/male ratio was 4.8/1. Two hundred thirty two of surgeries were performed by all surgeons in the department between 2009 and 2012. One hundred eleven out of 343 patients were provided by two surgeons who have been involved in the field of endocrine surgery after 2012. Mean follow up period was 6.4±0.6 months.

In group P there were 26 patients while group T consisted of 317 patents. Table 1 shows the demographic and clinical characteristics of the patients in both groups. Demographic variables and patients characteristics including age, sex and history of hyperthyroidism were similar in both groups (Table 1). Pre-operative total serum calcium levels of patients in groups T and P did not differ significantly (p=0.32). Asymptomatic or symptomatic hypocalcemia (the presence of clinical symptoms of hypocalcemia such as tingling and numbness, Chvostek's sign, Trousseau's sign and/or total serum calcium laboratory levels < 8 mg/dL) was seen in 37 (10.7%) patients. This included 33 patients (10.4%) from group T and 4 patients (15.3%) from group P (p=0.45). Nodule size was comparable in both groups (p=0.08) (Table 1).

The mean age of patients with hypocalcemia was 44.2±11.3 years, the mean age of patients who did not developed hypocalcemia was 48.6±12.4 years (p=0.04). In univariate analysis of age for hypocalcemia p value was also 0.04 (Table 2). Within the described periods, the rate of IPs after total thyroidectomy (TT) (3.7%, n=4) was lower after 2012, compared to previous (10.4%, n=22) period (p=0.04). Although, the IP rate was lower for surgeons who were specialized in endocrine surgery compared to other surgeons, surgeon factor did not show any

statistical correlation with the development of hypocalcemia on univariate analysis (p=0.72). In addition, univariate analysis showed that sex, hyperthyroidism parameters, IP and nodule size were not predictive for postoperative transient and permanent hypocalcemia (Table 2 and 3, respectively). On multivariate analysis, all factors including IP, did not reveal any statistically significant correlation with postoperative transient hypocalcemia (Table 2). A multivariate analysis was not performed for permanent hypocalcemia as p value was higher than 0.3 for all parameters (Table 3).

The total number of patients with PG autotransplation was 11. Seven of these were performed in 2009-2012 period and 4 of these were performed in 2012-2013 period (p=0.77). One patient in each period experienced temporary hypocalcemia (p=45). No any permanent hypocalcemia was seen on these eleven patients with autotransplantation.

The incidence of post-operative hypocalcemia was investigated among patients in whom IP occured (n=26). Pre-operative total serum calcium levels were <8.4 mg/dL in four of these patients, however postoperative symptomatic hypocalcemia developed in only one of them. On the contrary, 3

Table 3: Univariate analysis of factors affecting post-operative permanent hypocalcemia in patients with standardized surgery

Parameter	p value univariate	OR* univariate
Age	0.95	0.99
Gender**	0.28	N/A***
Dominant nodule size	0.37	0.95
Inadvertent parathyroidectomy	0.49	N/A***
Hyperthyroidism	0.33	1.04
Surgeon factor	0.97	N/A***

* OR: Odds Ratio
**As only one parameter was <0.3 multivariate analysis was not performed
***N/A: Not Applicable

Table 1: Demographics of the groups

Parameter	Group T (n=317)	Group P (n=26)	p value
Age (years, median)	48 (20-81)	43 (28-74)	0.63
Gender Female (n/%) Male (n/%)	 260/82 57/18	 24/92.3 2/7.7	 0.14
Hyperthyroidism (n/%)	84/26.4%	5/19.2%	0.65
Dominant nodule size (cm, mean ± SD)	3.3±1.8	2.7±1	0.08
Presence of subcentimetric nodules (n/%)	20/6.3%	2/7.6%	0.83
Pre-operative total serum calcium (mg/dL, mean ± SD)	8.9±0.8	8.8±0.6	0.32
Post-operative total serum calcium (mg/dL, mean ± SD)	8.3±0.7	8.1±0.8	0.27
Total serum calcium at 6th month (mg/dL, mean ± SD)	8.8±0.4	8.7±0.3	0.28
Post-operative transient hypocalcemia* (n/%)	33/10.4%	4/15.3%	0.45
Post-operative permanent hypocalcemia (n/%)	3/0.9%	0/0%	0.49
Mean follow-up period (months, mean ± SD)	6.4±0.6	6.5±0.6	0.81

*The patients with asymptomatic and symptomatic hypocalcemia, SD: Standard deviation

Table 2: Univariate and multivariate analysis of factors affecting post-operative transient hypocalcemia in patients with standardized surgery

Parameter	p value univariate	OR* univariate	p value multivariate**	OR multivariate**
Age	0.04	0.97	0.13	0.56
Gender	0.28	0.55	0.34	0.97
Dominant nodule size	0.19	0.98	0.22	0.98
Inadvertent parathyroidectomy	0.45	0.63	N/A***	
Hyperthyroidism	0.38	0.61	N/A***	
Surgeon factor	0.72	0.87	N/A***	

*OR: Odds Ratio, **Multivariate analysis was performed for the parameters whose p<0.3, ***N/A: Not Applicable

out of 22 patients, in whom pre-operative total serum calcium levels were within the normal laboratory range developed post-operative transient hypocalcemia (p=0.73).

The number of PGs totally excised was 31 in 26 patients. The number of excised PGs was one in 21 of these patients and two in remaining 5 patients. Anatomical localization of excised PG were: right side in 17 of patients (54.8%), left side in 8 patients (25.8%), intrathyroidal in 3 cases (9.7%), and bilateral in 2 patients (6.5%). In one patient (3.2%), the PG was in an ectopic location (isthmus). The location of IP was not associated with hypocalcemia (p=0.14). Twenty one of accidentally removed PGs (67.7%) were at the adjacent side of the dominant thyroid nodule. The incidence of dominant nodule and excised PG did not correlate significantly with hypocalcemia (p=0.17). Postoperative transient hypocalcemia occured in 3 (14%) patients who had one gland removed and in 1 (20%) patient in whom two glands were removed (p=0.73). Permanent hypocalcemia developed in 3 patients in group T (0.9%), and in none of the patients in group P (Table 1).

Discussion

The indisputable role of thyroid surgery in the treatment of thyroid disorders in goiter- endemic regions such as Turkey has been defined (1). Recent surgical advances in thyroid surgery have led to an emphatic decrease in thyroid surgery related mortality and morbidity. While reported rates on mortality are around nil, the rates of major complications are below 5% (3). The major decrease in mortality and morbidity has been attributed to the increase in surgical experience over years (4,15,23-25).

In the current literature, the relationship between accidental parathyroidectomy and hypocalcemia is doubtful (26-28). Also, surgical experience, extent of surgery, previous surgical history, hyperthyroidism, young age, malignancy are potential risk factors for post-operative hypocalcemia and all these risk factors have been broadly discussed in the last 2 decades (3,4). In a recently published study by Lorenta-Poch et al. (22), the authors recommended the Parathyroid Glands Remaining *In Situ* (PGRIS) classification system which is based on the number of '*in-situ* preserved' parathyroid glands. PGRIS scores were found to be inversely related with the development of post-operative hypocalcemia (p<0.001). In our study, inadvertent parathyroidectomies reported in final histopathology report were included to group P, Therefore, group T includes the cases with IP and parathyroid auto-transplantation which were considered as "four parathyroid gland preserved" during thyroidectomy. Eleven of the patients had PG autotransplantation in our serie and two of them had temporary hypocalcemia. On their follow-up, any of these autotransplanted patients had permanent hypocalcemia.

Postoperative hypocalcemia may last for less than six months (transient) or more (permanent). Its reported incidence varies from center to center and range between 1.6% and 50%, with most of the reported cases being transient in nature (17-19,29). In our study, mean follow up time was 6.4±0.6 months and was similar in both group (p=0.81). Transient hypocalcemia rate in all patients was 10.8% and permanent hypocalcemia rate in all patients was 0.8%. In group P, there was no permanent hypocalcemia. However; in group T, the rate of permanent hypocalcemia rate was 0.9%. This may also be related with ischemia of the PG or related factors rather than the number of remaining PGs.

The prevention and management of iatrogenic hypocalcemia should include the correct selection of patients who are at a higher risk for postoperative hypocalcemia, identification of the PGs during thyroidectomies, and a careful application of the surgical technique. Intraoperative pathologic verification of inadvertent PG removal during thyroid surgeries may be necessary. Previously published reports suggest intra-muscular auto transplantation of accidentally removed PGs that are encountered peri-operatively (22,30-32). An appropriate and timely fashioned management of postoperative hypocalcemia that may occur as a result of accidental removal of PGs is warranted to ensure better patients outcomes and protection of the surgeon against medico-legal issues.

Risk factors for IP, as described in the literature include young age, hyperthyroidism, malignant diseases, previous surgical history and lymph node dissection (14-17). Other factors include bilateral surgical procedures and extent of surgery (33). Four-gland exploration of parathyroid glands may predispose the PGs to surgical trauma thus leading to vascular compromise of the PGs (6,22). Our study therefore focused on patients who underwent standard bilateral thyroidectomies and investigated the incidence of accidental parathyroidectomies. Thyroid surgeries are usually performed for the treatment of benign thyroid disorders which are prevalently seen in young patients. Most of the patients enrolled into the study consisted of young adults, specifically young female adults in their reproductive age. Demographic characteristics of both groups including age and sex, showed a homogenous distribution (p=0.14 and p=0.63, respectively). However, younger age was relevant with post-operative hypocalcemia in univariate analysis (p=0.04).

The incidence of bleeding has been reported to be high in thyroid surgeries for hyperthyroidism (13). This condition has been associated with difficult visualization of the PGs during thyroid surgeries (3,13). Also, attempt to control bleeding during thyroid surgeries may predispose the PGs to ischemia. In our study, hyperthyrpoidism was not a predictive factor of post-operative hypocalcemia in both groups.

Thyroid surgery for malignancy, may increase the risk of inadvertent PTs. Specifically, the risk of accidental

parathyroidectomies has been reported to be high in patients who undergo central neck dissection for thyroid cancers (17-19,24,25). Resection of malignant tumors that invade the capsule and surrounding tissues may also predispose patients to IPs during thyroid surgeries. This can also result in the destruction of the vascular supply of the PGs thus leading to postoperative hypocalcemia. The risk of IP is also pronounced in recurrent cases that undergo re-operative surgery. Our study excluded all patients who underwent thyroid surgeries for the treatment of known thyroid malignancies and those who were operated on for recurrent disease.

Surgical experience is known to play an important role in reducing mortality and morbidity rates after thyroid surgeries (4). Within the study period, the incidence of IPs after BTT, was 3.7% (4 of 111 patients) in surgeons specialized in endocrine surgery, compared to 10.4% (22 of 232 patients) in surgeons practising general surgery only (p=0.04). Although, a higher rate of IP was seen among surgeons practising in general surgery only, on multivariate analysis, surgeon factor did not show any statistically significant corrrelation with the development of hypocalcemia (p=0.72).

The relationship between the dominant nodule and IP has been recently investigated by Yazici et al. (6). In this study, IP mostly occurred on the same side as the dominant nodule. This finding was associated with the changed location of the PG due to the adjacent enlarged nodule or its close anatomical relation with the fibrous capsule surrounding the thyroid gland. In our study, the correlation between dominant nodule side and IP side was also investigated. Similarily, in group P, 67.7% of IPs (n=21) occurred on the dominant nodule side. However, this result did not correlate with hypocalcemia (p=0.17). The side of IP itself did not correlate with hypocalcemia (p=0.14) either.

Adaptive mechanisms that occur in the body after sub-total parathyroidectomy have not been well investigated. In healthy individuals undergoing thyroid surgeries, the accidental removal of one or two PGs has been associated with permanent hypocalcemia as a complication (17,25). Nevertheless, studies investigating the actual effect of total or subtotal parathyroidectomy on calcium hemostasis are lacking in the medical literature. Hence, the awareness of the attending surgeon should be drawn to a patients who are at an increased risk for post-operative hypocalcemia. According to our study results, number of excised PGs did not correlate significantly with postoperative hypocalcemia (p=0.73).

Study Limitations

In this retrospective chart review, we sought to investigate the incidence of IPs at a tertiary hospital serving an endemic population with thyroid disorders. Additionally, factors predictive of IPs and their association with postoperative hypocalcemia were evaluated. The major limitation of our study was the retrospective design. A prospective study for IP based on the similar base criteria and similar case standardization might reveal a better and more accurate results for its effects on hypocalcemia. Also a larger number of case in each group with a longer follow up period may lead more detailed statistical analysis in terms of univariate and multivariate regression models. As a result, the incidence of hypocalcemia was found to be higher in group P, however, this was not statistically significant when compared to that of group T (p=0.45). The similar rates of incidence of hypocalcemia between groups could be attributed to the fact that, although most of the parathyroid glands were intact in group T, their vascularization may have been compromised as a result of surgery.

Our study shows that, when the extent of surgery and hyperparathyroidism are excluded, surgical experience also plays a major role in the reduction of incidence of IPs which occurs during standardized bilateral total thyroidectomies. In our study, younger age was relevant with post-operative hypocalcemia and it was significant in univariate analysis but not an independent risk factor yet.

Conclusion

In contrary to previous reports, factors such preoperative hyperthyroidism, dominant nodule size, and number of excised glands did not have a significant correlation with the development of postoperative hypocalcemia.

Ethics

Ethics Committee Approval: In terms of anonymized data usage for the study, no local ethics committee approval was obtained.

Informed Consent: A written informed consent for total thyroidectomy was received from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.C.D., C.A., M.F.Ç., M.G.Ü., Concept: A.C.D., S.B., Design: A.C.D., C.A., Data Collection or Processing: S.B., H.T., Analysis or Interpretation: Y.O., H.A., Literature Search: M.F.Ç., M.G.Ü., Writing: A.C.D., C.A.,

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