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Investigation of the effect of perioperative parathyroid autotransplantation in incidental parathyroidectomy cases on the development of postoperative hypocalcemia: a retrospective observational study

Metin Bozkaya[1], Ebru Menekşe[2], Hikmet Pehlevan Özel[3], Yasir Keçelioğlu[4], İbrahim Doğan[5]

[1]Department of General Surgery, Soma State Hospital, Soma, Türkiye
[2]Department of General Surgery, Ankara City Hospital, Ankara, Türkiye
[3]Department of General Surgery, Mamak State Hospital, Ankara, Türkiye
[4]Department of General Surgery, Yeşilyurt Hasan Çalık State Hospital, Malatya, Türkiye
[5]Department of General Surgery, Başkale State Hospital, Van, Türkiye

Purpose: One of the most common and significant complications following thyroid surgery is postoperative hypocalcemia due to postoperative hypoparathyroidism. This study aimed to observe the effect of parathyroid gland autotransplantation on postoperative hypocalcemia in cases of incidental parathyroidectomy in total thyroidectomy cases.
Methods: Patients who underwent bilateral total thyroidectomy surgery were retrospectively analyzed. Patients in the study population were divided into group A (no incidental parathyroidectomy), group B (incidental parathyroidectomy with no autotransplantation), and group C (incidental parathyroidectomy with autotransplantation). The patients' calcium levels on day 1, transient and permanent hypocalcemia times, time to return to normocalcemia, and surgery duration were examined.
Results: A total of 647 patients meeting the research criteria were included in the study. Group A consisted of 443 patients (68.5%), group B consisted of 176 patients (27.2%), and group C consisted of 28 patients (4.3%). The rate of incidental parathyroidectomy in the entire patient population was 31.5% (n = 204). Transient and permanent hypocalcemia rates in the entire patient population were 27.7% (n = 178) and 0.6% (n = 4), respectively. It was observed that the frequency of day 1 hypocalcemia was higher in group B than in group C among incidental parathyroidectomy groups (P = 0.005). Furthermore, group B had a significantly higher frequency of transient hypocalcemia compared to group C (P = 0.006). There was no significant difference in terms of permanent hypocalcemia.
Conclusion: This study showed that parathyroid gland autotransplantation reduces transient hypocalcemia in patients with 2 or fewer incidental parathyroids.
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Key Words: Hypocalcemia, Parathyroidectomy, Thyroidectomy

INTRODUCTION

Thyroid surgery is frequently performed for benign or malignant reasons in thyroid gland diseases. One of the most common and significant complications following thyroid surgery is postoperative hypocalcemia due to postoperative

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Corresponding Author: Metin Bozkaya
Department of General Surgery, Soma State Hospital, Turgutalp Mahallesi, Bergama Caddesi No. 225, Manisa 45500, Türkiye
Tel: +90-236-6131973
E-mail: drmbozkaya@gmail.com
ORCID: https://orcid.org/0000-0003-2490-6627

hypoparathyroidism. Hypocalcemia leads to an extension of the patient's hospitalization and necessitates additional biochemical assessments [1,2]. Therefore, factors influencing postoperative hypocalcemia in patients undergoing total thyroidectomy have been extensively researched in the literature [3,4].

Postoperative hypoparathyroidism is reflected in the patient's biochemical values as a gradual decrease in parathyroid hormone levels during the postoperative period. This is often associated with impaired blood supply to the parathyroid gland or parathyroid gland resection [5,6]. In the literature, the rates of temporary hypocalcemia vary between 1.2% and 40% in different series. The rates of permanent hypocalcemia are approximately 0%–3% [7-10]. The incidence of incidental parathyroidectomy in case series in the literature has been reported to be between 22% and 35.5% [11-13].

The most important way to prevent permanent hypoparathyroidism and permanent hypocalcemia in thyroidectomy surgery is the meticulous preservation of parathyroid glands. However, in practice, even for high-volume surgeons, achieving this can be challenging, especially in thyroid surgeries with added neck dissection. Incidental parathyroidectomy is observed in pathology reports at a rate of 3-30% even in operations performed by experienced surgical teams [14]. Some studies have attempted to predict incidental parathyroidectomy risk factors and transient hypocalcemia [15]. Despite numerous studies, a consensus has not been reached on predisposing factors and the high-risk patient group that leads to this condition [13]. Therefore, the autotransplantation of devascularized or incidentally removed parathyroids is commonly performed. In fact, some authors have practiced routine autotransplantation because they believe that autotransplanted parathyroid glands are more controlled in terms of vascularization and nutrition than parathyroid glands left in place [6,16]. Some studies have indicated that the number of incidentally removed parathyroids, specifically 2 or fewer, does not have an impact on permanent hypocalcemia [17]. However, the relationship between the number of incidentally removed parathyroids, the impact of autotransplanted parathyroids on parathyroid function, and the recovery of parathyroid function remains unclear [18,19].

The purpose of this study was to observe the effect of parathyroid gland autotransplantation on postoperative hypocalcemia in cases of incidental parathyroidectomy in total thyroidectomy cases.

METHODS

Ethics statement

Our study received ethical approval from the Ethics Committee of Ankara City Hospital (No. E1-22-2632) on June 01, 2022. Patient enrollment began after obtaining ethical approval. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Informed consent was obtained from all individual participants included in the study.

Study design

The study was designed as retrospective observational research. The patient population was determined using the database of Ankara City Hospital from January 2018 to December 2020. Patient privacy was strictly maintained during the creation of the patient population and data screening, with no information sharing with third parties outside the research team.

Study population

The study included patients who were 18 years or older, both male and female, who had undergone bilateral total thyroidectomy (including those who had undergone central and/or lateral neck dissection), had no previous thyroid and/or parathyroid surgery, and had at least 1 year of regular follow-up in the database. Patients with a history of neck radiotherapy, concurrent parathyroid disease and those receiving calcium replacement therapy due to additional metabolic diseases were excluded.

Study procedure

In the center where the study was conducted, the surgical indications for all patients were determined by a multidisciplinary council consisting of endocrinology, general surgery, and nuclear medicine clinics during the preoperative period. Surgical operations were performed by experienced, high-volume surgeons specialized in thyroid surgery. A total of 655 patients meeting the study criteria were identified based on patients' surgical notes and pathology reports, and they were divided into 3 main groups for further analysis.

Group A was formed from patients whose surgical notes did not mention perioperative incidental parathyroidectomy, and no incidental parathyroidectomy was reported in the postoperative pathology report. Group B was composed of patients whose surgical notes did not mention perioperative incidental parathyroidectomy, but incidental parathyroidectomy was reported in the postoperative pathology report. Group C was created from patients whose surgical notes indicated the non-viability of the parathyroid gland perioperatively or the presence of the parathyroid gland noticed by the surgeon, leading to parathyroid gland autotransplantation, and no incidental parathyroidectomy was reported in the postoperative pathology report. Patients who underwent autotransplantation were included in the study if the procedure followed the autotransplantation technique described by Wells et al. [20] in

1975. In this technique, the incidentally removed parathyroid gland is dissected into small pieces using a scalpel and implanted by separating the ipsilateral sternocleidomastoid muscle. The aim is to provide nutrition to the parathyroid gland through diffusion.

Incidental parathyroidectomy was defined as parathyroid glands autotransplanted due to disrupted perioperative blood supply or noticed in the specimen by pathology. Eight patients with more than 3 incidentally removed parathyroid glands were excluded from the study.

Data and outcome measures

Patients were evaluated for age, sex, preoperative toxic condition, operative time, postoperative pathological diagnosis, number of incidental parathyroid glands, location of autotransplantation if performed, and whether central neck dissection was performed. Biochemically, corrected calcium levels were examined in the preoperative period, on postoperative day 1, at 6 months postoperatively, and 1 year postoperatively. Additionally, preoperative albumin, thyroid-stimulating hormone (TSH), and 25-OH vitamin D values were assessed. For autotransplanted patients, the month from which calcium levels returned to normal during follow-up was determined. Transient hypocalcemia was defined as hypocalcemia that normalized within the first year after the operation, while permanent hypocalcemia was defined as hypocalcemia lasting longer than 1 year. The duration of transient hypocalcemia has been defined differently in studies. A period of 6 to 12 months has been defined for transient hypocalcemia in various studies [11,20]. However, permanent hypocalcemia has been defined as hypocalcemia that cannot be treated for 1 year after surgery. Therefore, in our study, all cases of hypocalcemia that resolved within 1 year were defined as transient hypocalcemia. The normal range for calcium was set as 8–10.4 mg/dL, while other biochemical parameters were assessed based on the normalization of clinical biochemical parameters. Patients who underwent surgery received calcium replacement therapy according to current treatment protocols during the postoperative period.

Statistical analysis

All analyses were performed using IBM SPSS Statistics ver. 21 (IBM Corp.). The normal distribution of numerical data was checked with the Kolmogorov-Smirnov test. Numerical variables were presented as mean ± standard deviation (SD), median, and range, while categorical variables were presented as number (n) and frequency (%). Continuous numerical variables were analyzed using a 1-way analysis of variance or Student t-test. For categorical variables, chi-square analysis or Fisher exact test was performed. A P-value of <0.05 was considered statistically significant.

RESULTS

A total of 647 patients who met the research criteria were included in the study. Among these patients, 160 were male (24.7%), and 487 were female (75.3%). The mean age of the patients was 50.8 ± 12.81 years.

In the entire patient population, the rate of incidental parathyroidectomy was 31.5% (n = 204). Among the patients, 24.3% (n = 157) had 1 incidental parathyroid gland removed, and 7.3% (n = 47) had 2 incidental parathyroid glands removed. In the entire patient population, the rates of transient and permanent hypocalcemia were 27.7% (n = 178) and 0.6% (n = 4), respectively. Patients were divided into 3 groups: group A comprised 443 patients (68.5%), group B had 176 patients (27.2%), and group C had 28 patients (4.3%).

There was a similar distribution of age among the groups (P = 0.353). Significant differences were observed in terms of sex distribution among the groups (P = 0.029). *Post hoc* tests revealed that the difference was mainly due to group B, where the proportion of female patients was statistically significantly higher than in group C (P = 0.042, Bonferroni correction applied). No differences were observed in terms of preoperative calcium (P = 0.358), preoperative albumin (P = 0.468), preoperative TSH (P = 0.966), preoperative vitamin D (P = 0.295), and preoperative toxic condition (P = 0.051).

Significant differences were found in terms of postoperative pathological malignancy (P = 0.029). *Post hoc* tests showed that the difference was mainly between group A and group B, where the rate of postoperative pathological malignancy was higher in group B (P = 0.036, Bonferroni correction applied).

There were differences in terms of the rates of central dissection (P < 0.001). *Post hoc* tests revealed that the difference was between group A and group B, as well as between group A and group C. Group B had a higher rate of central dissection compared to group A (P < 0.001, Bonferroni correction applied). Group C had a higher rate of central dissection compared to group A (P < 0.001, Bonferroni correction applied) (Table 1).

The groups with incidental parathyroidectomy (groups B and C) were evaluated in terms of demographic and clinicopathological data. A similar age distribution was observed among the groups (P = 0.24). The female patient population was higher in group B (P = 0.014). There were no differences observed in terms of preoperative calcium (P = 0.373), preoperative albumin (P = 0.363), preoperative TSH (P = 0.714), preoperative vitamin D (P = 0.289), preoperative toxicity status (P = 0.118), postoperative pathological malignancy (P = 0.422), and central dissection rates (P = 0.856).

All groups were compared in terms of postoperative outcomes. Significant differences were observed in the frequency of 1st-day hypocalcemia between the groups (P < 0.001). *Post hoc* tests revealed that the difference was between

Table 1. Demographic and clinicopathological characteristics of groups (n = 647)

Characteristic	Group A	Group B	Group C	P-value
No. of patients	443	176	28	
Age (yr)	50.38 ± 13.02	49.82 ± 12.46	46.86 ± 11.61	0.353
Sex				0.029*
Female	327 (73.8)	143 (81.3)	17 (60.7)	
Male	116 (26.2)	33 (18.8)	11 (39.3)	
Preoperative findings				
Calcium (mg/dL)	9.46 ± 0.44	9.49 ± 0.43	9.57 ± 0.33	0.358
Albumin (g/dL)	45.50 ± 3.43	45.84 ± 2.76	45.33 ± 2.56	0.468
TSH (mU/mL)	1.90 ± 8.56	2.07 ± 3.54	1.81 ± 1.46	0.966
Vitamin D (ng/mL)	19.28 ± 11.21	20.09 ± 13.11	24.12 ± 15.11	0.295
Toxicity status				0.051
Nontoxic	373 (84.2)	161 (91.5)	23 (82.1)	
Toxic	70 (15.8)	15 (8.5)	5 (17.9)	
Pathological malignancy				0.043*
No malignancy[a]	367 (82.8)	132 (75)	20 (71.4)	
Malignancy[b]	76 (17.2)	44 (25)	8 (28.6)	
Patients with central dissection	15 (3.4)	29 (16.5)	5 (17.9)	<0.001***

Values are presented as number only, number (%), or mean ± standard deviation.
Group A, without incidental parathyroidectomy; group B, incidental parathyroidectomy with no autotransplantation; group C, incidental parathyroidectomy with autotransplantation.
TSH, thyroid-stimulating hormone.
[a]Benign ± microinvasive carcinoma; [b]malignant ± invasive carcinoma.
*P < 0.05, ***P < 0.001.

Table 2. Comparison of postoperative outcomes among groups

Hypocalcemia	Group A (n = 443)	Group B (n = 176)	Group C (n = 28)	P-value
First-day hypocalcemia				<0.001***
No	359 (81.0)	82 (46.6)	21 (75.0)	
Yes	84 (19.0)	94 (53.4)	7 (25.0)	
Temporary hypocalcemia				<0.001***
No	361 (81.7)	83 (48.0)	21 (75.0)	
Yes	81 (18.3)	90 (52.0)	7 (25.0)	
Permanent hypocalcemia				0.097
No	442 (99.8)	173 (98.3)	28 (100)	
Yes	1 (0.2)	3 (1.7)	0 (0)	
Surgery duration (min)	111.21 ± 47.07	117.47 ± 48.08	124.64 ± 53.22	0.152

Values are presented as number (%) or mean ± standard deviation.
Group A, without incidental parathyroidectomy; group B, incidental parathyroidectomy with no autotransplantation; group C, incidental parathyroidectomy with autotransplantation.
***P < 0.001.

group A and group B and between group B and group C. In group B, the frequency of 1st-day hypocalcemia was higher than in group A (P < 0.001, Bonferroni correction applied). In group B, the frequency of 1st-day hypocalcemia was higher than in group C (P = 0.015, Bonferroni correction applied).

There was a significant difference in the frequency of temporary hypocalcemia (P < 0.001). *Post hoc* tests showed that the difference was between group A and group B and between group B and group C. In group B, the frequency of temporary hypocalcemia was higher than in group A (P < 0.001, Bonferroni correction applied). In group B, the frequency of temporary hypocalcemia was higher than in group C (P = 0.018, Bonferroni correction applied). There was no significant difference among the groups regarding permanent hypocalcemia (P = 0.097).

Furthermore, a significant difference was observed among the groups in terms of the time to reach normocalcemia during the postoperative period (P < 0.001). In group A, mean calcium recovery time was measured as 0.20 ± 0.55 months; in group B, 0.72 ± 1.31 months; and in group C, 0.28 ± 0.53 months.

Post hoc tests revealed that the difference was between group A and group B, and in group B, the time to normocalcemia was statistically significantly longer than in group A ($P < 0.001$, Bonferroni correction applied). There were no significant differences among the groups in terms of the duration of surgery (Table 2).

The incidental parathyroidectomy groups (groups B and C) were evaluated in terms of postoperative outcomes. Group B had a higher frequency of hypocalcemia on the 1st day ($P = 0.005$). Group B had a higher frequency of temporary hypocalcemia ($P = 0.006$). There were no significant differences among the groups in terms of permanent hypocalcemia ($P = 0.641$), time to normocalcemia ($P = 0.082$), and surgery duration ($P = 0.471$).

Groups B and C were evaluated in terms of the average number of incidental parathyroid glands. In group B, the mean number of incidental parathyroid glands was measured as 1.20 ± 0.40, while in group C, it was measured as 1.39 ± 0.49. As a result of the evaluation, it was observed that the average number of incidental parathyroid glands in group C was significantly higher than that in group B ($P = 0.028$).

DISCUSSION

In today's medical practice, thyroidectomy surgery is one of the most common surgical procedures. Therefore, the importance of high-quality studies on the diagnosis and treatment of potential complications has increased. Torabi et al. [21] demonstrated that postoperative hypocalcemia has an impact on the patient's need for temporary or permanent medication, length of hospital stays, and complications associated with hypocalcemia.

In the study, the factors that could affect hypocalcemia were homogenized. All case groups were operated on by the same surgical team in a single center. When the average surgery times were evaluated considering all patients, no significant difference was found between the groups (Table 2). It was observed that there was no significant difference in the preoperative values affecting the calcium levels of the patients (Table 1). However, despite all this, in future studies, the effect of autotransplantation can be observed more significantly by selecting the patient groups in more detail in terms of the factors affecting hypocalcemia and by making prospective planning.

One of the most frequently observed specific complications following thyroidectomy surgery is hypocalcemia. In a study by Doulaptsi et al. [12], it was found that the rate of temporary hypocalcemia was significantly higher in patients who had 2 or fewer incidental parathyroid glands removed, which is consistent with the current study. However, in the mentioned study, the duration for permanent hypocalcemia was set at 6 months, while in our study, this duration was determined as 1 year. We believe that this difference in the duration may be associated with the lower rate of permanent hypocalcemia in this study.

A study by Su et al. [22] compared patients with papillary thyroid carcinoma who underwent total thyroidectomy and neck dissection, with or without parathyroid autotransplantation. It was found that temporary hypocalcemia was significantly higher in patients who had undergone autotransplantation of 1, 2, or 3 parathyroid glands compared to those who did not receive autotransplantation. However, there was no significant difference in permanent hypocalcemia rates. In a study by Wang et al. [18], significant differences were found in hypocalcemia within the first 24 hours between patients who had received autotransplantation of 1 parathyroid gland and those who had not, but no significant difference was observed in permanent hypocalcemia rates. It was suggested that this might be related to the continued functionality of the preserved 3 parathyroid glands. In a study by Palazzo et al. [23], they found that permanent hypocalcemia after total thyroidectomy did not significantly differ between groups regardless of the number of transplanted parathyroid glands, but temporary hypocalcemia was significantly higher in patients who had undergone transplantation of 2 or more parathyroid glands. Therefore, it was suggested that the transplantation of a single parathyroid gland might be unnecessary. These studies demonstrate the impact of the number of compromised or removed parathyroid glands on temporary hypocalcemia. Özden et al [17] showed that the presence of 2 or fewer incidental parathyroids in postoperative specimens did not affect permanent hypocalcemia.

Unlike the other studies mentioned above [18,22,23], in this study, not only were cases of incidental parathyroidectomy with autotransplantation considered, but cases of incidental parathyroidectomy without autotransplantation were also evaluated as a separate group. The study included cases of 2 or fewer incidental parathyroidectomies, with or without transplantation. Postoperative outcomes in the study were initially evaluated among all groups and then among the incidental parathyroidectomy groups. Additionally, unlike the mentioned studies, the incidental parathyroidectomy groups were compared among themselves.

In a retrospective study by Tartaglia et al. [19] aimed at observing the postoperative effects of parathyroid autotransplantation in 244 patients, the initial 3-day serum calcium levels were found to be significantly higher in patients with no parathyroid glands detected, as compared to cases where autotransplantation was performed or incidental parathyroids were found but not transplanted. However, no significant difference was found in the rate of improvement of hypocalcemia between patients with incidental parathyroidectomy and those with autotransplantation.

In a prospective study by Lorente-Poch et al. [6] involving 669 patients, postoperative serum calcium values were found to be similar between the group with parathyroid autotransplantation and the group without it. The incidence of temporary and permanent hypocalcemia was similar in both groups, with no significant differences. In this study, a lower frequency of temporary hypocalcemia was observed in the autotransplantation group, but no significant difference was noted in terms of permanent hypocalcemia.

The imbalances in the number of patients between the groups in the study can be considered among the limitations of the study. This situation is especially evident in the sample group (group C). However, when the current situation is considered based on the incidental parathyroidectomy rates, the incidental parathyroidectomy rate of the study (groups B and C) shows a rate of 31.5%. This rate is similar to current literature sources [14]. The low number of patients in group C is related to the practices in the clinic where the study was conducted and is a limitation of the study. Although the number of patients cannot be increased due to the retrospective study, this obstacle will be overcome by extending the study period in future studies.

Other limitations of the study include its retrospective nature, a limited number of cases for comparing permanent hypocalcemia, lack of homogenization in terms of sex and malignancy, and the inability to standardize postoperative dilutional hypocalcemia.

In addition, due to the retrospective nature of the study, there are limitations in observing the long-term effects of autotransplantation and the effects of autotransplantations performed on the forearm or other localization. Preventing these in future studies will yield more valuable results. However, there are very few studies in the literature that include a group of incidental parathyroidectomy cases without autotransplantation. In this regard, this study can pave the way for new assessments and research on this topic.

This study demonstrated that parathyroid autotransplantation in patients with 2 or fewer incidental parathyroids significantly reduces temporary hypocalcemia. However, parathyroid autotransplantation is a simple surgical procedure that does not extend the operation time and can be considered in cases where the viability of the remaining parathyroid glands cannot be assured. Further research on methods to assess the viability of the intraoperative parathyroid gland will also contribute to determining the necessity of parathyroid autotransplantation in this patient group.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

ORCID iD

Metin Bozkaya: https://orcid.org/0000-0003-2490-6627
Ebru Menekşe: https://orcid.org/0000-0003-2867-6128
Hikmet Pehlevan Özel: https://orcid.org/0000-0002-9146-3742
Yasir Keçelioğlu: https://orcid.org/0000-0002-7561-1741
İbrahim Doğan: https://orcid.org/0000-0001-7413-1837

Author Contribution

Conceptualization: MB, EM, HPÖ
Formal analysis: MB, EM
Methodology: EM, HPÖ
Data curation: MB, YK, İD
Supervision: HPÖ
Writing – Original Draft: MB
Writing – Review & Editing: MB, EM, YK, İD

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