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Original Research

# Does the Risk of Hypocalcemia Increase in Complementary Thyroidectomy Performed in Papillary Thyroid Cancer?

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## Abstract

**Objectives:** Papillary thyroid cancer (PTC) is the most common type of thyroid cancers. In some patients, due to the histopathological features of PTC, complementary thyroidectomy (CT) may be needed to contralateral thyroid lobe after lobectomy. Hypocalcemia is the most common complication after thyroidectomy and its etiology is multifactorial. It is still controversial whether the CT increases the risk of hypocalcemia or not. In this study, we aimed to evaluate whether CT procedure increases the risk of hypocalcemia compared to total thyroidectomy (TT) in PTC patients.

**Methods:** The data of the patients who were operated between 2015 and 2018 and diagnosed with PTC in the pre-operative or post-operative period were evaluated retrospectively, and two patient groups were formed. Group 1 included 19 patients who were diagnosed with PTC in the pathological examination after lobectomy was performed in the first operation, and after that CT was performed to the contralateral lobe. Among the patients who were diagnosed with pre-operative or post-operative PTC in the same period, 53 patients with characteristics similar to the 1st group in terms of age and gender were selected for Group 2. Biochemical parameters related to calcium metabolism in the pre-operative and post-operative periods, parathyroid autotransplantation and unintentional parathyroid gland removal, post-operative hypocalcemia, and treatment rates were compared between the two groups.

**Results:** There were 19 patients (13 F and 6 M) with a mean age of 48.3±12.1 years and 53 patients with a mean age of 46.3±9 (40 F and 13 M) in Groups 1 and 2, respectively, and there was no significant difference between the groups in terms of age and gender. There was no significant difference in terms of pre-operative parathormone (PTH), phosphorus (P), magnesium (Mg), Vitamin D deficiency rate, parathyroid autotransplantation, and presence of parathyroid gland in thyroid specimen. Pre-operative calcium (Ca) value was 9.33±0.46 in Group 1 and lower than Group 2 (9.65±0.41) (p=0.012). There was no significant difference between the groups in terms of post-operative day 0 Ca, P, Mg, and PTH and post-operative day 1 Ca, Mg, and PTH. Post-operative day 1 P level was significantly lower in Group 1 (2.86±0.72) compared to Group 2 (3.6±0.83). Post-operative hypocalcemia rates were 21.1% and 30.2% in Groups 1 and 2, respectively, and the difference was not significant (p=0.558). In both groups, hypocalcemia was transient and permanent hypoparathyroidism was not detected. Parathyroid autotransplantation rates (10.5% vs. 3.8%; p=0.283) and the rate of unintentionally removed parathyroid gland (0 vs. 15.1; p=0.185) were similar in Groups 1 and 2, respectively. Ca and active Vitamin D administration rates in the post-operative period were similar in Group 1 and Group 2 (10.5% vs. 22.6%; respectively), and there was no significant difference between the groups in terms of receiving treatment (p=0.327).

**Conclusion:** CT can be necessary in some patients with post-operative diagnose of PTC. CT can be performed without increased risk of hypocalcemia compared to TT.

**Keywords:** Complementary thyroidectomy, Hypocalcemia, Papillary thyroid cancer, Total thyroidectomy, Transient hypocalcemia

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Papillary thyroid cancer (PTC) is the most common thyroid cancer and its primary treatment is surgery. Most of PTC patients are low-risk group patients and extent of surgical treatment is still controversial due to the low mortality risk. In recent years, it is noteworthy that more conservative surgical strategies have been recommended to minimize the potential morbidity of wide surgical resection.[1] In 2009, total thyroidectomy (TT) was recommended as the first choice for tumors larger than 1 cm in the ATA guideline.[2] After that, in 2015, lobectomy was recommended as the first choice for tumors smaller than 1 cm, in addition, lobectomy was considered appropriate for tumors between 1 cm and 4 cm without extrathyroidal extension and lymph node metastasis in ATA guideline. Furthermore, lobectomy is recommended as the first surgical intervention in patients with indeterminate fine-needle aspiration biopsy (FNAB), especially in unilateral lesions <4 cm.[3] After the 2015 ATA guideline, the rate of TT has decreased and the rate of lobectomy has increased in the treatment of thyroid cancer in the USA.[4]

Complementary thyroidectomy (CT) for the contralateral lobe may be required in approximately 25% of patients after lobectomy in nodules with indeterminate FNAB due to the detection of malignancy in the pathology and in approximately 50% of patients after lobectomy in low-risk PTC.[5,6]

It has been reported that the complication rate is lower in lobectomy compared to TT.[7] CT can be performed for residual or recurrent thyroid cancer, for recurrent benign thyroid disease, and for removal of the contralateral lobe in patients with malignancy in histopathological examination after lobectomy is performed.[2,8] Secondary interventions are technically difficult due to anatomical distortion, scar, edema, and friability; and the complication risk is higher than primary thyroid surgery in a operated thyroid site.[8] Since the opposite lobe is not explored in lobectomy, it is still a matter of debate whether CT performed after lobectomy increases complications, especially hypocalcemia, which is the most common complication.[5,9]

Although there are many studies on post-thyroidectomy in the literature, the number of studies on the effect of CT on hypocalcemia and other complications is limited. In this study, we aimed to evaluate whether CT with the diagnosis of PTC increases the risk of hypocalcemia compared to total thyroidectomy.

## Methods

Data of patients who were operated between 2015 and 2018 with the diagnose of PTC preoperatively or postoperatively were evaluated retrospectively after ethical consent was obtained from local ethic committee (Date: February 16, 2021, Number: 3139). Informed consent was obtained from the patients that their medical data would be used in academic studies. Two groups were formed as CT group (Group 1) and total thyroidectomy group (Group 2). Group 1 includes 19 patients. These patients had pre-operative indeterminate biopsy result (Bethesda 3,4,5), Bethesda 1 result twice, Bethesda 2 results, and PTC detected in the other nodule; and these are patients who underwent lobectomy according to FNAB results and then CT for postoperative histopathological results. Group 2 included 53 patients who were diagnosed preoperatively and underwent total thyroidectomy in the same period, with similar age and gender characteristics as Group 1.

*Exclusions Criteria:*

- Patients who had had subtotal thyroidectomy and after that underwent thyroidectomy due to PTC development in remnant thyroid tissue,
- Patients who had adjacent organ resection due to macroscopic extrathyroidal extension,
- Patients who had central neck dissection,
- Patients who had lateral neck dissection,
- Patients who had surgery due to recurrent PTC,
- Patients who had clinical findings related to hypoparathyroidism before surgery.

Thyroidectomy technique: In our clinic, thyroidectomy is performed under general anesthesia with a standard Kocher incision. Thyroidectomy is performed with intraoperative nerve monitoring routinely, and the other technical details were given in our other studies.[10-12]

Surgical loupes are used routinely while performing thyroidectomy. In thyroidectomy, the tertiary branches of the inferior thyroid artery were separated on the thyroid capsule, and parathyroid glands were tried to be visualized in the dissection area, usually in normal localization areas.[13] If no parathyroid gland can be observed in the dissection area, no additional dissection was performed to reveal.

The number of parathyroid glands observed defines the total number of parathyroids observed in first lobectomy and CT in Group 1.

An unintentionally removed parathyroid or devitalized parathyroid gland during thyroidectomy was kept in saline during the surgery to be autotransplanted. The removed parathyroid gland was chopped into 1 mm3 pieces and buried into the sternocleidomastoid muscle on the same side and marked with a Prolene suture.[14]

CT was performed after 1–4 months later from the first surgery. The same previous Kocher incision was used for performing CT. It was applied by opening between the midline strep muscles and entering the thyroid lodge. Lateral dissection of the thyroid lobe was performed as in primary thyroidectomy.

Pre-operative serum calcium (Ca), phosphorus (P), magnesium (mG), parathormone (PTH), and 25-hydroxyvitamin D3 (25(OH)vitD3) levels of the patients were noted. Serum Ca, P, Mg, and PTH levels were measured at post-operative 4th h and post-operative 1st day. Vitamin D deficiency was defined as serum 25(OH)Vitamin D level below 20 ng/ml.[15] Post-operative 1st day calcium (Ca) value of <8 mg/dl was defined as biochemical hypocalcemia, and symptoms accompanying biochemical hypocalcemia were defined as symptomatic hypocalcemia.[16] Post-operative 4th h PTH value below 15 ng/L was defined as hypoparathyroidism.[17] Treatment was applied in patients with symptomatic hypocalcemia or patients with PTH value below 15 ng/L.

Hypocalcemia treatment: In our clinic, patients were treated with calcitriol (0.25–1 × 2–3 mcg/day) and elemental calcium (1–2 g × 3/day) if the PTH value of <10 pg/mL or findings of symptomatic hypocalcemia developed; treatment was arranged according to the severity of symptoms, calcium level, in patients with elemental calcium (1–2 g × 3/day) treatment, and PTH values of 10–15 pg/mL. In addition, intravenous calcium (10 mL 10% calcium gluconate ampoule) treatment was given in patients with calcium level below 7 mg/dl and/or severe hypocalcemia symptoms, in additionally. Intravenous calcium therapy was continued until adjusted total serum calcium level increased above 7.5 mg/dL and/or severe hypocalcemia symptoms regressed. Patients with mild symptoms with a calcium value of 7.5 mg/dl or asymptomatic patients with calcium values above 7 mg/dl were discharged.

Pre-operative TSH, anti-Tg, anti-TPO, and biochemical parameters related to calcium metabolism in the pre-operative and post-operative period, parathyroid autotransplantation, and unintentionally parathyroid gland removal, post-operative hypocalcemia, and hypocalcemia treatment rates were compared between the two groups.

## Statistical Analysis

SPSS was used for statistical analysis of data (Statistical Packages for the Social Sciences, software, edition 21, SPSS Inc., Chicago, USA).

For numerical variables, mean, standard deviation, and number and percentage for categorical variables were specified. Pearson Chi-square test or Fisher's exact test was performed for comparison of the groups and differences between the ratios of categorical variables; non-parametric comparisons were calculated with the Mann–Whitney U-test. P<0.05 was accepted statistically significant.

# Results

There was no significant difference between Groups 1 and 2 in terms of age and gender. Furthermore, there was no significant difference in terms of pre-operative PTH, P, Mg, Vitamin D deficiency rate, parathyroid autotransplantation, and presence of parathyroid gland in thyroid specimen, too. Pre-operative TSH level was significantly higher in Group 1 than Group 2 (3.6±3.6 uIU/mL vs. 1.7±1.3 uIU/mL, p=0.004, respectively). Pre-operative Ca value was lower in the 1st group than in the 2nd group (p=0.012) (Table 1). There was no significant difference between the values of post-operative day 0 Ca, P, Mg, and PTH; day 1 Ca, Mg, and PTH (Table 2). On post-operative day 1, P level was significantly lower in Group 1 than in Group 2. (2.86±0.73 mg/dl vs. 3.60±0.83 mg/dl, respectively; p=0.003). Post-operative hypocalcemia rates were 21.1% and 30.2% in Groups 1 and 2, respectively, and the difference was not significant (p=0.558). In both groups, hypocalcemia was transient and permanent hypoparathyroidism was not detected. The rate of administration of Ca and sometimes active Vitamin D in the post-operative period was 10.5% in Group 1 and 22.6% in Group 2, and there was no significant difference between the groups in terms of receiving treatment (p=0.327).

# Discussion

Hypocalcemia is the most common complication after thyroidectomy and its etiology is multifactorial.[18,19] In a meta-analysis includes 115 observational studies, median incidence was reported 27% for transient hypocalcemia and 1% for permanent hypocalcemia.[19] It is still debatable that CT increased or decreased hypocalcemia or comparable in terms of hypocalcemia compared to the TT.[5,9]

In CT procedure, a fibrous tissue can be encountered while opening between the strep muscles. This area is not dangerous for dissection. After this region is opened, the lateral and posterolateral of the thyroid lobe where the parathyroid glands and RLN are topographically located are the virgin region, and dissection can be performed in this region as in primary surgery.

In our study, although the rate of transient hypocalcemia was 20.1% in the CT group and 30.2% in the TT group, the difference between the two groups was not significant (p=0.558). According to the results of this study, CT does not increase transient hypocalcemia compared to TT. Day 1 P level was lower in the CT group compared to the TT group (2.86±0.73 mg/dl vs. 3.60±0.83 mg/dl, respectively, p=0.003). Since phosphorus ion is inversely related to calcium, although the difference in terms of hypocalcemia is not statistically significant, it may be related to the lower rate of hypocalcemia in the CT group. In some studies, no

**Table 1.** Comparison of pre-operative and perioperative data of Groups 1 and 2

| | Group 1 (n=19) | Group 2 (n=53) | p |
|---|---|---|---|
| Pre-operative data | | | |
| Age (mean±SD) | 48.3±12.1 | 46.3±9 | 0.622* |
| Gender (n: F/M) | 13/6 | 40/13 | 0.550** |
| Pre-op TSH (uU/mL) (mean+SD) | 3.6±3.6 | 1.7±1.3 | 0.004* |
| Pre-op anti-TPO (U/mL) (mean±SD) | 64±117 | 68±148 | 0.685* |
| Pre-op anti-Tg (U/mL) (mean±SD) | 182±253 | 115±324 | 0.345* |
| Pre-op Ca (mg/dL) (mean±SD) | 9.32±0.46 | 9.64±0.41 | 0.012* |
| Pre-op P (mg/dL) (mean±SD) | 3.18±0.89 | 2.88±1.06 | 0.273* |
| Pre-op Mg (mg/dL) (mean±SD) | 1.87±0.25 | 1.78±0.71 | 0.817* |
| Pre-op PTH (pg/mL) (mean±SD) | 47.47±17.17 | 50±25.89 | 0.971* |
| Pre-op Vit D (ng/mL) (mean±SD) | 22.68±14.52 | 14.17±8.77 | 0.027* |
| Pre-op Vit D deficiency <20 (%) | 52.9 | 64.5 | 0.433** |
| Perioperative data | | | |
| Number of parathyroid glands perioperative detected (%) | | | 0.155* |
| 0 | 5.3 | | |
| 1 | 5.3 | 1.9 | |
| 2 | 31.6 | 15.1 | |
| 3 | 10.5 | 20.8 | |
| 4 | 47.4 | 62.3 | |
| Parathyroid autotransplantation (%) | 10.5 | 3.8 | 0.283* |
| Parathyroid gland on specimen (%) | 0 | 15.1 | 0.185* |

Pre-op: Pre-operative, TSH: Thyroid-stimulating hormone, TPO: Thyroid peroxidase, Tg: Thyroglobulin, SD: Standard deviation, Ca: Calcium, P: Phosphorus, Mg: Magnesium, PTH: Parathyroid hormone, Vit D: Vitamin D, Mann–Whitney U-test: *, Pearson Chi-square test (or Fisher's exact test): **, mean±SD: Mean ±standard deviation.

**Table 2.** Comparison of post-operative data of Groups 1 and 2

| | Group 1 (n=19) | Group 2 (n=53) | p |
|---|---|---|---|
| Post-op day 0 Ca (mg/dL) (mean±SD) | 8.53±0.74 | 8.54±0.54 | 0.711* |
| Post-op day 0 P (mg/dL) (mean±SD) | 3.07±0.73 | 3.26±0.91 | 0.391* |
| Post-op day 0 Mg (mg/dL) (mean±SD) | 1.87±0.57 | 1.75±0.49 | 0.984* |
| Post-op day 0 PTH (pg/mL) (mean±SD) | 37.37±18.61 | 28.18±20.85 | 0.077* |
| Post-op day 1 Ca (mg/dL) (mean±SD) | 8.70±0.64 | 8.49±0.74 | 0.133* |
| Post-op day 1 P (mg/dL) (mean±SD) | 2.86±0.73 | 3.60±0.83 | 0.003* |
| Post-op day 1 Mg (mg/dL) (mean±SD) | 1.86±0.17 | 1.87±0.19 | 0.693* |
| Post-op day 1 PTH (pg/mL) (mean±SD) | 36.26±22.99 | 22.17±18.54 | 0.307* |
| Hypocalcemia n (%) | 4 (21.1) | 16 (30.2) | 0.558* |
| Hypocalcemia treatment n (%) | 2 (10.5) | 12 (22.6) | 0.185 |

Post-op: Post-operative, SD: Standard deviation, Ca: Calcium, P: Phosphorus, Mg: Magnesium, PTH: Parathyroid hormone, Mann–Whitney U-test: *, Pearson Chi-square test (or Fisher's exact test): **, mean±SD: Mean ±standard deviation.

significant difference was detected in between CT and TT in terms of transient and permanent hypocalcemia.[20,21] In another study, permanent hypoparathyroidism was not detected in both the CT and TT groups; in addition, although transient hypocalcemia rates were similar in both groups, total complication rate was detected significantly higher in TT group compared to lobectomy and CT groups (7% vs. 3% vs. 0; p=0.002; respectively).[22] On the other hand, both Park et al. (9.4% vs. 26.6%; P = 0.031) and Giordano et al. (14.8% vs. 25.6% p=0.0057, respectively) reported a lower rate of transient hypoparathyroidism in CT than in TT.[23,24] Dedhia et al. determined the rate of transient hypoparathyroidism with PTH <10 pg/mL in the early post-operative period to be lower in the CT group than in TT (6% vs.14.3%, respectively; p=0.009).[25] Similarly, Merchavy et al. reported transient hypocalcemia lower in CT than in TT (1.5% vs. 12.5%, respectively; p=0.02).[9]

Although there is no consensus regarding a lower rate of hypocalcemia in patients undergoing CT, it has been suggested that this may be related to the time interval between the first surgery and CT. It is explained by the fact that the interval time allows time for the revascularization of the possibly devitalized parathyroid glands in the first lobectomy surgery.[9] In accordance with this claim, in the study of Dedhia et al., post-operative early serum PTH values in the CT group compared to the TT group (39 pg/mL vs. 24 pg/mL; p<0.001, respectively) and PTH levels at the 2nd week (44 pg/mL vs. 32 pg/mL; p=0.022) were higher.[25]

In our study, pre-operative PTH levels were similar between the two groups (CT: 47.47±17.17 vs. TT: 50±25.89; p=0.971). Although there was no statistical difference between PTH levels on post-operative day 1, PTH levels were higher in the CT group (CT: 36.26±22.99 vs. 22.17±18.54, p=0,307). It suggests the fact that more than 1 month elapsed time between surgeries is an important factor in the recovery of parathyroid vascularization and function in the operated side. The timing of CT after lobectomy is also a matter of debate.

Glockzin et al. recommended that CT should be performed in the first 3 days after the first surgery or after 3 months later from the first surgery to reduce perioperative morbidity.[26] El-Sharaky et al., on the other hand, showed that the functions of the devascularized parathyroids generally improved within 4 weeks after surgery.[27]

Giordano et al. detected the rate of transient hypoparathyroidism to be higher in the TT group in multivariate analysis and also determined TT as an independent risk factor (p=0.0046, OR (95%CI): 0.482 (0.291–0.798). In addition, female gender (p=0.0021; OR [95%CI]: 1.979 [1.280–3.058]) and number of parathyroid glands remaining in situ (PGRIS) ([higher vs. lower scores] p<0.0001 OR [95%CI]: 0.429 [0.296–0.621]) were determined as another independent risk factors for transient hypoparathyroidism. For permanent hypoparathyroidism, only the number of PGRIS ([higher vs. lower scores] p=0.0001 OR [95%CI]: 0.401 [0.251–0.640]) was determined as independent risk factor.[23]

In present, number of PGRIS is considered as critical factor for preventing from post-operative hypoparathyroidism according to the evidences of studies.[28] Parathyroid gland autotransplantation and unintentionally resected parathyroid glands are the main factors affecting PGRIS. In our study, there was no difference between two groups in terms of parathyroid gland autotransplantation and unintentionally resected parathyroid glands. The effect of parathyroid gland autotransplantation to hypocalcemia is still controversial.

Parathyroid gland autotransplantation increases the risk of early hypoparathyroidism, the rate of hypoparathyroidism is correlated with the number of autotransplanted parathyroid glands, and the rate of hypoparathyroidism increases as the number of autotransplanted glands increases.[29-31]

Today, the contribution of parathyroid gland autotransplantation to the prevention of permanent hyperparathyroidism is one of the most controversial issues. Some studies recommend liberal or routine parathyroid gland autotransplantation in the belief that it can prevent permanent hypoparathyroidism.[32] However, other studies have reported that the rate of permanent hypoparathyroidism in patients who underwent parathyroid gland autotransplantation does not decrease or may even increase.[33] A recent meta-analysis demonstrated that unintentionally resection of (accidental removal) parathyroid gland increases both transient and permanent hypoparathyroidism.[34]

In most studies, no difference was reported between TT and CT in terms of permanent hypoparathyroidism, transient and permanent recurrent laryngeal nerve palsy (RLN), wound infection, and hematoma.[5,20,21,24,25]

Sawant et al., on the other hand, reported the rate of permanent RLN paralysis in the CT performed side 1% and hypocalcemia requiring more than 6 months of treatment in 8% of the patients, although the overall complication rate after CT was 14%. The authors emphasized that although the rate of early complications in CT is minimal, the risk of permanent complications that will have a serious impact on quality of life is significant and should be considered carefully before the CT decision.[35] In similar, Shaha et al. also suggested that, according to the observations on patients, CT procedure is more risky and CT decision should be made carefully.[35]

The limitations of our study are that it is single center and retrospective, and the number of cases is limited. However, the biochemical follow-ups for hypocalcemia, the selection of age and gender, and similar patients in groups with PTC are the positive aspects of the study.

As a result, CT may be necessary in some patients with a post-operative histopathological diagnosis of PTC. CT can be performed without increasing the risk of hypocalcemia compared to TT.

### Disclosures

**Ethics Committee Approval:** This study conformed to the Helsinki Declaration. The study was approved by the local ethics committee (Date: February 16, 2021, Number: 3139).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – M.T.U., M.U., O.C.; Design – M.T.U., N.A., O.C.; Supervision – N.A., M.U.; Data collection &/or processing – O.C., M.K., M.T.U.; Analysis and/or interpretation – N.A., M.U., O.C.; Literature search – M.T.U., M.U., N.A.; Writing – M.T.U., N.A., M.K.; Critical review – N.A., M.T.U., M.U.

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