Postprint of a Study on the Pattern of Serum Calcium Changes After Total Thyroidectomy

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Abstract

Objective: To investigate the functional recovery of autotransplanted parathyroid glands by studying the patterns of serum calcium changes in patients who underwent total thyroidectomy with transplantation of four parathyroid glands.

Methods: Twenty-one patients who underwent total thyroidectomy with intraoperative autotransplantation of four parathyroid glands performed by the same surgical team at Peking Union Medical College Hospital between April 2012 and January 2016, and who completed one-year follow-up, were selected. Repeated measures analysis of variance was used to compare total venous serum calcium levels at 48 hours, 1 week, 1 month, 6 months, and 1 year postoperatively with preoperative levels and to analyze their changing trends.

Results: Compared with preoperative levels, serum calcium levels were significantly decreased at 48 hours postoperatively (1.83 vs. 2.28 mmol/L, P=0.00). At 1 week postoperatively, calcium levels began to recover and reached preoperative levels (2.23 vs. 2.28 mmol/L, P=0.14). At 1 month, 6 months, and 1 year postoperatively, calcium levels were 2.28, 2.27, and 2.25 mmol/L respectively, with no significant differences compared with preoperative levels (P>0.05).

Conclusion: In patients with autotransplantation of four parathyroid glands, serum calcium levels decrease significantly at 48 hours postoperatively, then gradually recover and remain stable long-term, suggesting that autotransplanted parathyroid function begins to recover from 1 week postoperatively and can be maintained long-term.

Full Text

Study on the Pattern of Blood Calcium Changes After Total Thyroidectomy

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Abstract

Objective: To investigate the functional recovery of autotransplanted parathyroid glands by examining the pattern of blood calcium changes in patients who underwent total thyroidectomy with four parathyroid autotransplants.

Methods: We retrospectively identified 21 patients who underwent total thyroidectomy performed by the same surgical team at Peking Union Medical College Hospital between April 2012 and January 2016, with intraoperative autotransplantation of four parathyroid glands and complete one-year follow-up data. Repeated measures ANOVA was used to compare serum total calcium levels at 48 hours, 1 week, 1 month, 6 months, and 1 year postoperatively with preoperative baseline levels.

Results: Compared with preoperative levels, serum calcium decreased significantly at 48 hours postoperatively (1.83 vs. 2.28 mmol/L, P=0.00). Calcium levels began to recover by 1 week postoperatively and reached preoperative levels (2.23 vs. 2.28 mmol/L, P=0.14). No significant differences were observed between preoperative and postoperative levels at 1 month, 6 months, or 1 year.

Conclusion: In patients receiving four parathyroid autotransplants, serum calcium levels decrease significantly at 48 hours postoperatively, then gradually recover and remain stable long-term, suggesting that autotransplanted parathyroid function begins to recover within one week postoperatively and can be maintained long-term.

Keywords: Thyroidectomy; Hypoparathyroidism; Parathyroid autotransplantation; Hypocalcemia

Introduction

The increasing incidence of thyroid cancer has become a global phenomenon [1, 2], with surgery being the most common and effective treatment modality. Total thyroidectomy is the most frequently performed procedure. In China, the incidence of postoperative hypoparathyroidism after total thyroidectomy can reach 4.3% [3]. A nationwide Korean study involving over 190,000 cases reported that the incidence of permanent hypoparathyroidism could reach approximately 5% [4]. These data indicate that a considerable number of patients undergoing thyroid cancer surgery develop permanent hypoparathyroidism, underscoring the importance of preventing and managing this complication.

Careful patient selection for total thyroidectomy, meticulous surgical dissection with in situ preservation of parathyroid glands, and autotransplantation of parathyroid glands that cannot be preserved in situ are all effective measures to reduce postoperative permanent hypoparathyroidism. Although numerous studies recommend routine autotransplantation when parathyroid glands cannot be preserved in situ [5-9], few have directly demonstrated that transplanted parathyroid glands survive and function to reduce the incidence of postoperative hypoparathyroidism. The incidence of short-term postoperative hypocalcemia in thyroid patients ranges from 1.6% to 68% [10, 11]. Some studies suggest that fresh parathyroid tissue implanted into muscle pockets requires 6-8 weeks to restore normal function before calcium levels gradually increase [12]. Palazzo et al. [13] reported that most patients could discontinue calcium supplementation only after 2-3 months postoperatively (when blood calcium reaches >2.0 mmol/L). However, sufficient evidence regarding the true functional recovery pattern of transplanted parathyroid glands remains lacking.

Most individuals have four parathyroid glands [5, 14]. Therefore, we selected patients with thyroid cancer who underwent total thyroidectomy with transplantation of all four parathyroid glands and studied their postoperative blood calcium changes. Through quantitative analysis of calcium changes in patients with complete parathyroid transplantation, we aimed to elucidate the functional changes of transplanted parathyroid glands and provide evidence for clinical management of postoperative hypoparathyroidism.

Subjects and Methods

1. Study Subjects We retrospectively reviewed 756 patients who underwent total thyroidectomy performed by the same surgical team at Peking Union Medical College Hospital between April 2012 and January 2016. Patients who received four parathyroid autotransplants confirmed by intraoperative frozen section pathology were identified. Postoperatively, patients with severe numbness or tetany received immediate intravenous calcium gluconate (1-2 g, repeated as

needed for recurrent tetany) along with routine oral calcium supplementation (Caltrate D 600 mg twice daily). Rocaltrol (0.25 g once or twice daily) was added when necessary. Patients without obvious symptoms but with serum calcium <2.0 mmol/L also received routine oral calcium supplementation. Calcium and Rocaltrol were gradually discontinued once serum calcium increased to 2.0 mmol/L.

Initial inclusion criteria: (1) Patients undergoing initial total thyroidectomy with four parathyroid autotransplants; (2) Patients with regular preoperative and postoperative calcium monitoring and complete clinical-pathological data. **Exclusion criteria:** (1) Patients who did not receive calcium supplementation and had serum calcium >2.0 mmol/L at 48 hours postoperatively; (2) Patients who did not complete one year of regular follow-up.

2. Data Collection Clinical and pathological data were collected for all included patients, including age, sex, surgical procedure, pathological findings, postoperative hypocalcemia symptoms, calcium supplementation details, and serum calcium levels at preoperative baseline, 48 hours, 1 week, 1 month, 6 months, and 1 year postoperatively.

3. Statistical Methods Serum calcium levels exhibited a positively skewed distribution and approximated normal distribution after logarithmic (lg10) transformation. Geometric means with 95% confidence intervals were used to describe average calcium levels. Repeated measures ANOVA was used to compare calcium levels across different time points, with $P<0.05$ considered statistically significant. All analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago), and graphs were created using GraphPad Prism 6 software (GraphPad Software Inc., San Diego).

Results

1. General Patient Characteristics During the study period, 42 patients (5.6% of all surgical patients) received four parathyroid autotransplants. After excluding 5 patients who did not receive calcium supplementation and had serum calcium >2.0 mmol/L at 48 hours, 37 patients met initial inclusion criteria. Twenty-one patients had complete one-year follow-up data and were included in the final analysis. Their clinical information is described in Table 1 .

Table 1 Clinical Information of 21 Included Patients

Characteristic	n (%)
Preoperative comorbidities	
Hyperthyroidism	
Chronic thyroiditis	
Surgical procedure	

Characteristic	n (%)
Total thyroidectomy + bilateral central neck dissection	
Total thyroidectomy + bilateral central neck dissection + unilateral level II/III/IV lateral neck dissection	
Postoperative pathology	
Papillary thyroid carcinoma	

A total of 13 patients (61.9%) developed hypocalcemia symptoms within 48 hours postoperatively, with 8 cases (38.1%) occurring on postoperative day 1 and 5 cases (23.8%) on day 2. Four patients (19.0%) experienced tetany, while 9 (42.9%) had only paresthesia. Eight patients (33.3%) received intravenous calcium supplementation (3g, 6g, 5g, 2g, 3g, 3g, 1g, and 2g of calcium gluconate, respectively) before transitioning to oral supplementation. All other patients received routine oral calcium supplementation, which was gradually reduced and discontinued at approximately 2-4 weeks postoperatively. Only 2 patients (9.5%) received Rocaltrol treatment (for 4 and 7 days, respectively). No patients required resumption of calcium supplementation due to recurrent hypocalcemia symptoms after tapering or discontinuation.

2. Blood Calcium and PTH Levels Serum calcium levels for all 37 patients are described in Table 2 .

Table 2 Blood Calcium Levels at Different Time Points in All Patients (mmol/L)

Time Point	95% CI
Preoperative	
48 hours postoperative	
1 week postoperative	
1 month postoperative	
6 months postoperative	
1 year postoperative	

Blood calcium levels for the final 21 included patients at each time point are shown in Table 3 .

Table 3 Blood Calcium Levels at Different Time Points in 21 Patients (mmol/L)

PTH levels were not measured preoperatively in any patient. At final follow-up, PTH levels were 28.27$±$11.60 pg/mL (range 21.9–57.6 pg/mL; normal range 12.0–68.0 pg/mL).

3. Comparison of Blood Calcium Levels at Different Time Points
Using preoperative calcium levels as the reference, logarithmically transformed (lg10) serum total calcium levels at 48 hours, 1 week, 1 month, 6 months, and 1 year postoperatively were compared using repeated measures ANOVA. Results showed that serum calcium levels decreased significantly at 48 hours postoperatively compared with preoperative levels (1.83 vs. 2.28 mmol/L, P<0.001). Calcium levels began to recover by 1 week postoperatively (P=0.14). No significant differences were found between preoperative and postoperative levels at 1 month (P=0.91), 6 months (P=0.59), or 1 year (P=0.06) (see Table 4 and Figure 1 [Figure 1: see original paper]).

Table 4 Comparison of Blood Calcium Levels at Different Time Points (mmol/L)

Time Point	Geometric Mean	95% CI	P-value*
Preoperative			
48 hours postoperative			
1 week postoperative			
1 month postoperative			
6 months postoperative			
1 year postoperative			

*Comparison of postoperative calcium levels with preoperative levels

Figure 1 Trend of Blood Calcium Level Changes

Discussion

Due to anatomical location and intraoperative manipulation, total thyroidectomy often inevitably injures parathyroid glands, leading to transient or permanent hypoparathyroidism. Meticulous dissection with in situ preservation of well-vascularized parathyroid glands is the preferred preventive measure. However, when parathyroid glands cannot be preserved in situ or their blood supply cannot be maintained, transplantation becomes necessary [5-7]. While numerous studies have demonstrated that parathyroid autotransplantation reduces postoperative hypoparathyroidism [8, 9, 15, 16], it remains difficult to distinguish whether gradual recovery of blood calcium levels results from functional recovery of in situ preserved glands or from transplanted glands. Furthermore, the timing and efficacy of transplanted parathyroid function remain controversial. Therefore, this study intentionally selected patients who underwent total thyroidectomy with four parathyroid autotransplants, using serum total calcium as an indicator of parathyroid function to analyze the recovery pattern of "completely transplanted" parathyroid glands. Through follow-up exceeding one year, we aimed to confirm the long-term efficacy of parathyroid autotransplantation

and provide reference for clinical management of postoperative hypoparathyroidism.

The number of parathyroid glands varies among individuals, ranging from 2 to 6, and in rare cases up to a dozen [17]. Anatomic data show that 84-93% of individuals have four parathyroid glands [14, 18]. To ensure consistency, this study included only patients who received four parathyroid autotransplants (42 cases) and excluded those who did not receive calcium supplementation and had serum calcium >2.0 mmol/L at 48 hours postoperatively (5 cases, 11.9%). This approach ensured the study could better reflect blood calcium changes after complete parathyroid transplantation. To investigate long-term outcomes, only patients with follow-up exceeding one year were included. Five patients with suspected supernumerary parathyroid glands (those with serum calcium >2.0 mmol/L at 48 hours) accounted for 11.9% of cases, consistent with reported literature [14, 18].

In patients undergoing total thyroidectomy with parathyroid preservation or autotransplantation, the lowest postoperative calcium levels typically occur at 48-72 hours [19], after which calcium levels gradually increase as preserved parathyroid function recovers and calcium supplementation is administered. Therefore, we selected 48 hours as a fixed early observation time point (with immediate calcium measurement and supplementation if patients developed severe hypocalcemia symptoms such as tetany). We also monitored calcium levels at 1 week, 1 month, 6 months, and 1 year to clarify medium- and long-term changes. Our results (Tables 3 and 4) showed that despite calcium supplementation, serum calcium levels at 48 hours postoperatively were significantly lower than preoperative levels (1.83 vs. 2.28 mmol/L, P<0.001). By 1 week postoperatively, while patients were still receiving calcium supplementation, calcium levels had markedly increased and approached preoperative levels (2.23 vs. 2.28 mmol/L, P=0.14), indicating that transplanted parathyroid glands had begun to function within one week postoperatively. Subsequently, patients gradually reduced calcium use, and by 1 month postoperatively, most had discontinued supplementation with calcium levels no different from preoperative levels (2.28 vs. 2.28 mmol/L, P=0.91), suggesting essentially complete parathyroid functional recovery. At 6 months and 1 year postoperatively, without calcium supplementation, calcium levels remained normal and parathyroid function remained stable, with no cases of permanent hypoparathyroidism. The longest follow-up times were >1.5 years in 8 patients, >2 years in 9 patients, and >3 years in 4 patients, with all maintaining stable calcium levels above 2.10 mmol/L. At final follow-up, all patients had PTH levels within our hospital' s normal range (21.9–57.6 pg/mL, 28.27$±$11.60 pg/mL). Even when including the 16 patients excluded from comparative analysis due to incomplete follow-up, similar trends in calcium level changes were observed across all 37 patients (Table 2). No patients required resumption of calcium tablets due to recurrent hypocalcemia symptoms. Therefore, autotransplantation of four parathyroid glands during total thyroidectomy can effectively preserve and restore parathyroid function, preventing permanent hypoparathyroidism. Moreover, this series of calcium monitoring results demon-

strates that transplanted parathyroid glands can begin functioning early, with essentially complete functional recovery by 4 weeks post-transplantation.

Previous studies have investigated the physiological activity of parathyroid glands transplanted into the brachioradialis muscle. Electron microscopic analysis of grafts at 1, 2, and 4 weeks postoperatively showed that transplanted parathyroid glands began to recover function at 1-2 weeks, with essentially complete recovery by 4 weeks [20]. Domestic researchers evaluated transplanted parathyroid activity by measuring PTH levels in ipsilateral cephalic vein blood, using contralateral cephalic vein blood as reference. Results showed increased PTH concentration differences between bilateral cephalic veins at 7 days postoperatively, with significantly higher PTH levels in the ipsilateral cephalic vein at 1 month, indicating biological activity of transplanted parathyroid glands [21]. However, these studies did not exclude the confounding effect of functionally recovering in situ preserved parathyroid glands, nor did they confirm whether active parathyroid grafts could meet normal physiological requirements. Our study minimized interference from non-transplanted glands by selecting patients with complete parathyroid transplantation and used serum calcium levels —a clinically relevant endpoint—as the evaluation metric, yielding time points consistent with previous research.

Another important consideration is the transplantation technique for optimal functional recovery. All patients in this study were operated on by the same surgical team using the following particle embedding method: First, sufficient parathyroid tissue (typically 1/4 to 1/3 of the gland) was obtained for frozen section diagnosis to confirm histological composition, while the remaining tissue was soaked in cold 0.9% saline solution. When feasible, confirmed parathyroid tissue was transplanted into muscle as soon as possible to minimize ischemia time. During transplantation, the parathyroid gland was cut into small pieces (approximately 1 mm × 1 mm × 1 mm) and implanted into a prepared pocket in the sternocleidomastoid muscle (ensuring no bleeding in the pocket), which was then closed with silk sutures (left as a marker). This technique is similar to those used in previous studies [22]. Our results demonstrate excellent parathyroid graft survival and confirm the effectiveness of this transplantation method.

This study has several limitations. First, we could not ensure that all parathyroid glands were transplanted in every included patient. Second, as a retrospective study, PTH levels were not routinely measured initially, so we lack direct data on parathyroid function changes over time. However, PTH levels were measured at final follow-up in all patients and were within normal range. Through inclusion and exclusion criteria, we minimized the inclusion of patients without complete parathyroid transplantation. Serum total calcium is convenient, accurate, inexpensive, and serves as the basis for postoperative hypocalcemia treatment (with the therapeutic target of raising calcium to 2.0 mmol/L to eliminate symptoms and avoid long-term complications). Therefore, we used serum total calcium as an indicator of parathyroid function.

In summary, we found that with routine calcium supplementation, most pa-

tients showed significant calcium level recovery at 1 week post-transplantation, allowing calcium dose reduction, with normalization to preoperative levels by 1 month. Calcium levels remained stable long-term after discontinuation of supplementation. This suggests that well-autotransplanted parathyroid glands begin to recover function approximately one week postoperatively, achieve near-complete functional recovery by one month, and can maintain function long-term.

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Note: Figure translations are in progress. See original paper for figures.