

The risk of hypocalcemia in patients with parathyroid autotransplantation during thyroidectomy

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ABSTRACT

Objective: Thyroidectomy is the most common cause of hypocalcemia. Preservation of parathyroid glands in situ is essential in preventing this complication. The aims of our study were to review patients who underwent parathyroid gland autotransplantation during thyroidectomy, and to compare hypocalcemia rates in patients with and without autotransplantation.

Material and Methods: Parathyroid gland autotransplantation was performed in 43 (7.9%) of 543 patients who underwent thyroidectomy between 2008 and 2012.

Results: Forty-four parathyroid glands were autotransplanted in 43 patients, including 36 women and 7 men. The median age was 55 (range: 30 to 68). The most common cause of autotransplantation was vascular compromise of the parathyroid gland. Early postoperative hypocalcemia developed in 37% of patients with autotransplantation, and none developed permanent hypocalcemia. Transient and permanent hypocalcemia rates were 9.6% and 0.4% in patients without autotransplantation, respectively. The risk of transient hypocalcemia was significantly high in patients with parathyroid autotransplantation ($p<0.001$). There was no difference between the two groups in terms of permanent hypocalcemia ($p=0.156$).

Conclusion: Despite meticulous dissection, parathyroid glands can be devascularized or removed inadvertently during thyroidectomy. Parathyroid autotransplantation is the best method to maintain parathyroid gland function. Although the risk of transient hypocalcemia is increased following parathyroid autotransplantation, long-term results are satisfactory.

Keywords: Parathyroid autotransplantation, hypocalcemia, thyroidectomy

INTRODUCTION

Thyroid surgery is the most frequently performed operation in general surgery clinics, and constitute 1% of all medical diseases (1). The second most feared complication of thyroid surgery, following recurrent laryngeal nerve (RLN) injury, is the development of hypocalcemia. The most common cause of hypocalcemia is post-surgery hypoparathyroidism (2). Hypocalcemia may develop in the immediate postoperative period and may improve in several weeks (transient hypocalcemia), or it may persist for more than 6 months after surgery, in which case is called permanent hypocalcemia. Hypocalcemia manifests with paresthesia, mental status changes, neuromuscular irritability, and muscle spasm. Chronic hypocalcemia can lead to cataract formation, calcification in the cerebellum and basal ganglia, peripheral neuropathy, and cardiac problems. These patients require lifelong calcium and vitamin D supplements.

Although subtotal thyroidectomy has been applied in the past to decrease the rate of thyroid surgery related complications, currently total and near-total thyroidectomy are the most frequently performed surgeries in benign multinodular goiter. This situation has led surgeons to pay more attention to preservation of the parathyroid gland function during surgery.

Although the rate of permanent hypoparathyroidism is reported between 0-43% in the literature, the current acceptable hypoparathyroidism rate in endocrine surgery is 1-2% (3, 4). The best way to avoid this complication is careful and meticulous dissection, ligation of the inferior thyroid artery branches separately at the thyroid capsule in order to prevent damage to parathyroid gland vascularization. Despite all precautions, unintentional parathyroidectomy during thyroidectomy can be detected at a rate of 9-19% (5). In the event of unintentional excision of the parathyroid glands or impairment of its vascular supply, the gland's functions may be preserved by parathyroid autotransplantation (PA).

The aim of this study was to determine hypocalcemia rates by reviewing thyroid patients with parathyroid autotransplantation during surgery, and to compare hypocalcemia rates in patients with and without autotransplantation.

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MATERIAL AND METHODS

Data of patients with parathyroid autotransplantation within 543 patients who underwent total or near-total thyroidectomy in Şişli Etfal Training and Research Hospital General Surgery Clinics between 2008-2012 were retrospectively analyzed. Indications for surgery, location of the removed parathyroid gland, the reason for autotransplantation and the number of autotransplanted glands, and presence of postoperative hypocalcemia were recorded. The rate of transient and permanent hypocalcemia in thyroidectomy patients without autotransplantation was also determined. Written consent was obtained from all patients before surgery. An ethics committee approval was obtained from the ethics committee of our hospital before the study.

Surgical Technique

Capsular dissection technique was applied in both total and near-total thyroidectomy. The recurrent laryngeal nerve was identified at the point where it crosses the inferior thyroid artery and was followed along its course and preserved. The artery and vein branches were ligated separately over the thyroid gland and transected. An extra dissection was not carried out during the operation to visualize the parathyroid glands. Parathyroid glands with impairment in vascular supply during capsular dissection, those localized in such a position that cannot be dissected without deterioration in vascular supply, and those located directly on the capsule were excised. If a darkening in the glands' color was detected during dissection, due to venous congestion, then the capsule was opened and the parathyroid glands regaining their normal color after drainage of venous blood were left in situ. In those where the color did not improve, the glands were excised. When in doubt, especially for malignant cases, the parathyroid tissue was confirmed by frozen section. After removing the specimens, they were carefully evaluated on the operating table, and if inadvertently removed parathyroid glands were identified they were excised for transplantation. The excised parathyroids were kept in physiologic saline. In the final stage of the operation, the parathyroid glands were sliced into pieces of 1x1 mm in size. Separated pockets were prepared within sternocleidomastoid muscle fibers on the same side for each 3-4 pieces. After the parathyroid slice was implanted in the pocket the muscle was closed with a 4/0 prolene suture and marked.

Postoperative follow-up

Post-operative paresthesia around the mouth and in the extremities, muscle spasms, Chvostek and Trousseau signs were evaluated from patient files. The routine calcium (Ca) and parathyroid hormone (PTH) measurements on postoperative 24 and 48 hours, 7 days, 1, 3 and 6 months were obtained from hospital records. Hypocalcemia was defined as a postoperative blood calcium (Ca) level below 8 mg/dL. Postoperative hypocalcemia for less than 6 months was defined as transient and those that lasted longer as permanent hypocalcemia. Patients who developed hypocalcemia and had a Ca value of 7-8 mg/dL were started on oral Ca preparations. Intravenous Ca gluconate was administered to symptomatic patients and those with a Ca value below 7 mg/dL. When symptoms resolved, and Ca level increased to >8 mg/dL, they were given oral treatment and active vitamin D. Calcium and PTH levels were observed daily until discharge in patients with hypocalcemia. Patients who were stabilized with treatment were discharged and followed-up in the outpatient clinic.

Statistical Analysis

The transient and permanent hypoparathyroidism rates in thyroidectomy patients with and without PA were compared by the Z test. The two groups were compared with chi-square and Fisher's exact test in terms of indications and extent of surgery. p values less than 0.05 were considered to be significant.

RESULTS

Parathyroid autotransplantation was applied in 43 patients out of 543 (7.9%) thyroidectomies. Thirty-six of the patients were female and seven were male. The median age was 55 years (30-68). The indication for surgery was multinodular goiter in 33 patients, thyroid cancer in 8 patients, and solitary nodules in 2 patients. Two patients underwent lobectomy and isthmectomy, 35 patients total thyroidectomy, and six patients underwent near total thyroidectomy. Central neck dissection was performed in four patients, and two patients underwent both central and lateral neck dissection (Table 1).

The excised parathyroid glands were the right lower glands in 15 patients, the left lower in 13, the right upper in 9, the left upper in 5, and in ectopic location in 2 patients. Two parathyroid glands were implanted in one patient (Table 2). Thirty-nine glands within the autotransplanted 44 parathyroid glands were thought to have vascular insufficiency. Two parathyroid glands that could not be separated from the thyroid and three parathyroid glands that were thought to be suspicious and were confirmed by frozen section were implanted into the muscle (Table 3).

Postoperative hypocalcemia developed within the first 2 days in 16 of 43 patients (37%) with autotransplantation, 11 of which required intravenous Ca infusion while five patients improved with oral Ca treatment alone. The median Ca value in patients with hypocalcemia was 7 mg/dL (6.1 to 7.9 mg/dL) and the PTH value was 13 pg/L (1-69 pg/L). At the end of six months, no permanent hypocalcemia was observed in any patient.

Table 1. Surgical indication and type of surgery

Indication	Patient number	Surgery
MNG	33	TT (27), NTT (6)
Thyroid cancer	8	TT+CND+LND
Solitary nodule	2	Lobectomy+isthmectomy

TT: total thyroidectomy; NTT:near total thyroidectomy; CND: central neck dissection; LND: lateral neck dissection

Table 2. Location of the excised parathyroid glands

Location	n
Right lower	15
Left lower	13
Right upper	9
Left upper	5
Ectopic	2

Table 3. Causes of parathyroid autotransplantation

Cause	n
Vascular impairment	39
Not being able to dissect from the thyroid	2
Suspicious gland	3

In the group without PA, the surgical indications were multinodular goiter in 388 patients, solitary thyroid nodules in 24, and thyroid cancer in 88 patients. There was no difference between the groups with and without autotransplantation in terms of surgical indications ($p=0.986$). In the group without autotransplantation, 420 patients underwent total thyroidectomy, 52 near-total thyroidectomy, and 28 patients underwent lobectomy. Twenty-nine patients underwent central, and six both central and lateral neck dissections. The two groups did not differ in terms of surgical extent ($p=0.754$). Within 500 patients who did not undergo PA, 48 (9.6%) developed transient and 2 (0.4%) had permanent hypocalcemia. The risk of development of transient hypocalcemia was significantly higher in patients who underwent autotransplantation as compared to those who did not ($p<0.001$). There was no significant difference between the two groups in terms of development of permanent hypocalcemia ($p=0.156$).

DISCUSSION

The rate of transient hypocalcemia after thyroid surgery was reported as high as 83%, and of permanent hypocalcemia as 43% (3). Factors influencing this rate include the skills and experience of the surgeon, good knowledge of the anatomy of the parathyroid gland, underlying thyroid pathology and the extent of resection (6, 7). Thyroid cancer, substernal and recurrent goiter, Grave's disease, thyrotoxicosis, lymphadenectomy are reported as main risk factors for the development of transient and permanent hypocalcemia (7-9).

Healthy parathyroid glands appear yellow-orange in color. The upper parathyroid glands are located at the level of the junction of 1/3 upper and middle parts of the thyroid gland, over the upper branch of thyroid artery posterolateral to the RLN. The lower parathyroids are located anterior to the RLN, within 2 cm of the inferior thyroid artery-RLN cross, but they can be detected in anywhere from the carotid bifurcation to the pericardium. The parathyroid glands are supplied through a single artery in 80%, and in 80%, this artery is a branch of the inferior thyroid artery. Thyroidectomy should be performed with capsular dissection technique, i.e. ligation of tertiary branches of the inferior thyroid artery separately on the thyroid capsule and mobilizing the parathyroid glands along with their blood vessels over the capsule in order to preserve parathyroid gland vascularization (10). The loss of parathyroid gland functions can also be the result of edema or hematoma due to inappropriate use of electrocautery. Inadvertent removal of the parathyroid glands may also lead to hypoparathyroidism and hypocalcemia (11). In 40-50% of such cases, it has been found that the parathyroid gland was located within the thyroid gland (12). It is usually reported that at least two glands should be injured for hypoparathyroidism to develop (13, 14).

However, normal looking parathyroid in its anatomic site does not always guarantee normocalcemia. Such a parathyroid gland may be detected to be avascular on pathologic examination and may not function postoperatively (14, 15). The issue on how to make sure of the function of the parathyroid gland is still controversial. Evaluation of the blood supply to the parathyroid capsule by making an incision, examination of blood flow by Doppler ultrasound, and intraoperative PTH measurements are within recommended methods in this regard. However, an ideal marker has not yet been identified (16). Therefore, parathyroid autotransplantation has been recommended whenever the function of the parathyroid gland is suspicious.

Lahey (17) has first proposed PA in 1926 in a case where the parathyroid gland was removed during subtotal thyroidectomy, in order to preserve its function. However, it did not attract interest for a long period until publication of successful biochemical and clinical outcomes of PA in patients with hyperparathyroidism in 1975 by Wells (18). Parathyroid autotransplantation can be performed in two ways to prevent permanent hypocalcemia. First, it can be applied immediately or in the delayed period during surgery in patients with hyperparathyroidism (2, 3). Second, it can be used routinely or selectively in thyroidectomy patients (4).

Parathyroid autotransplantation in case of an unintentionally removed parathyroid or a gland with impaired vascularization is the only option for the gland to function and is referred to as selective PA (4, 19). The development of permanent hypocalcemia despite all the attention and care encouraged surgeons to autotransplant one or more parathyroid glands during thyroidectomy, and it was reported that the rate of permanent hypoparathyroidism is decreased to below 1% with prophylactic routine autotransplantation (15, 20-23). There are two studies on the routine application of autotransplantation by Ohman (24) and Kihara (25). Ohman et al. compared patients where the glands were left in situ and those with autotransplantation of all visualized glands, and reported the permanent hypoparathyroidism rate as 43% in the group with autotransplantation. Kihara found the rate of permanent hypoparathyroidism in patients with autotransplantation as 21%, and reported that the PTH levels fall to 50% of the preoperative value in 5-year long-term follow-up. It is also noted that the routine practice of autotransplantation increases the rate of transient hypocalcemia in several studies (16, 26). However, there is no agreement in the literature on this subject. Testini (21) found the rate of transient hypocalcemia to be lower in the group that underwent routine autotransplantation than the group without (17% vs. 45%). In our study, the rate of transient hypocalcemia was 37% in the group with autotransplantation and 9.6% in patients without, and it was found that the difference was significant. There was no significant difference between the groups in terms of permanent hypocalcemia.

Palazzo et al. (16) reported that as the number of autotransplanted parathyroid glands increase the transient hypocalcemia rate also increased and they described the selective approach in PA rather than routine autotransplantation of well-vascularized parathyroid glands. In this approach, the threshold for selective treatment is low, autotransplantation

of the parathyroid gland that is considered to have a minor change in its pedicle and vascular supply is encouraged.

Promberger et al. (27) examined the role of parathyroid gland color change in showing its function, and they compared the control group where all four glands were visually normal with the group with two gland autotransplantation (group 2) and the group where despite serious discoloration in 3 or 4 glands the parathyroids were left in situ (group 3). They determined that the PTH and Ca levels improved more rapidly in the group with color change as compared to the group with autotransplantation. Thus, they reported that deterioration in color is not a good indicator of function and is the result of venous stasis and hemorrhagic infarction rather than impairment in arterial supply. Therefore, it was stated that if the pedicles were intact then the deterioration in color would be temporary.

Based on intraoperative PTH assays of 340 cases, Barczynski (26) reported that performing autotransplantation decreased the rate of transient hypocalcemia by half in comparison to the group with routine transplantation. They suggested autotransplantation for patients with a PTH level less than 10 at the end of the operation. Friedman (14) showed that the PTH level was less than 10 if the number of damaged parathyroids were three and above, and has proposed assessment of the parathyroid glands with biopsy and autotransplantation of those with impaired vascularization. However, despite its high sensitivity, it is known that a decreased intraoperative PTH does not guarantee development of hypocalcemia (26).

Trying to view the parathyroid glands during thyroidectomy is generally considered to be unnecessary (3). In addition, the effort for this cause increases the possibility of postoperative transient hypocalcemia (28, 29). Ideally, these glands should be preserved in their place without compromising vascularization. However, this is not always possible. Currently, there is no consensus on PA in order to maintain parathyroid gland function during thyroidectomy. However, autotransplantation of an unintentionally removed parathyroid or of a gland with impaired vascularity is the only option for the gland to function and is adopted by everyone. We also apply selective autotransplantation in our daily practice.

Since parathyroid re-exploration is usually not required after thyroidectomy, the preferred transplantation site is often the sternocleidomastoid muscle that can be accessed through the same incision, but transplantation into the pectoralis major and brachioradial muscles is also performed. In the generally preferred implantation method, 3-4 parathyroid tissue slices of 1 x 3 mm are being placed into separate pockets created within the muscle and the site is marked with suture or clips (4). A less preferred method is intramuscular injection of the finely chopped tissue buffered in 2 cc balanced saline in the form of a suspension (3). Pre-transplantation frozen section is often performed if there is doubt on whether the tissue is actually the parathyroid or not, or to avoid the possibility of malignant tissue implantation in patients with malignancy (7). Parathyroid glands may be confused with lymph nodes, thyroid tissue or fat tissue. Routine frozen examination is not always necessary both to maintain maximum parathyroid tissue and to avoid loss of time and increase in cost. It was reported that 93% of autotransplanted tissues without frozen section was actually the parathyroid (5).

The transplanted parathyroid tissue will spontaneously be re-vascularized and innervated. It begins functioning usually in 2-4 weeks and regains full function in two months (30, 31). In our series, we have seen that most cases with transient hypocalcemia improved within three months. We determine the function of the autotransplanted parathyroid gland with biochemical analysis. However, this does not always reflect the function of the graft within the sternocleidomastoid muscle, since the parathyroid tissue left in place continues to release hormones. In cases where the gland is grafted to the arm, a PTH value that is more than 1.5 times above the value from the other arm is an objective indicator of graft function (4).

CONCLUSION

Thyroid surgery is the greatest risk factor for developing hypocalcemia. Prevention of these complications by careful and meticulous dissection of the parathyroid glands, and their in situ conservation are important. Despite all the attention and care during thyroidectomy, the nutrition of the parathyroid glands may deteriorate or they may be unintentionally removed. In this case, PA is the best way to protect the gland's function. The outcome after autotransplantation is very good despite the high risk of transient hypocalcemia.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Şişli Etfal Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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