Recovery of Parathyroid Function After Total Thyroidectomy

MINORU KIHARA[1], HIROYASU YOKOMISE[1], AKIRA MIYAUCHI[2], and KENICHI MATSUSAKA[3]

[1] Second Department of Surgery, Kagawa Medical University, 1750-1 Miki-cho, Kita-gun, Kagawa 761-0793, Japan
[2] Kuma Hospital, 8-2-35 Shimoyamate-dori, Chuo-ku, Kobe 650-0011, Japan
[3] Higashiura Heisei Hospital, 1867 Kuruma, Higashiura-cho, Tsuna-gun, Hyogo 656-2351, Japan

Abstract: To prevent postoperative hypoparathyroidism following total thyroidectomy, the parathyroid glands are preserved in situ and/or resected or devascularized parathyroid glands are autotransplanted. We conducted a retrospective investigation utilizing biochemical and specific endocrine assessments to evaluate the difference in recovery of parathyroid function between the two operative methods. A total of 92 patients underwent total thyroidectomy at our hospital during the period between 1990 and 1997. These patients were divided into a preservation group ($n = 83$), with one or more preserved glands in situ, and an autotransplantation group ($n = 9$), with only transplanted glands. The level of intact parathyroid hormone (PTH) was completely restored by 1 year postoperatively in 83% (69/83) of the preservation group patients. In the remaining 14 patients (17%), the intact PTH had fallen below detectable levels on postoperative day (POD) 1, then subsequently recovered to 70% of the preoperative levels. Comparatively, in the autotransplantation group, the mean level of intact PTH recovered to only 43% of the preoperative levels. The results of this study suggest that parathyroid glands should be preserved in situ whenever possible, and that when intact PTH levels fall below detectable limits on POD 1, they may never recover to the preoperative levels in those patients.

Key Words: parathyroid gland, preservation, autotransplantation, total thyroidectomy, intact parathyroid hormone

Introduction

Postoperative hypoparathyroidism is a common iatrogenic complication following total thyroidectomy that subjects patients to a lifelong regime of calcium and α_1-vitamin D_3 supplements.[1–7] The incidence of latent

hypoparathyroidism, which is the inability to increase parathyroid hormone levels appropriately during a hypocalcemic challenge, is very high;[8,9] however, many reports state that parathyroid autotransplantation, being a method of transplanting removed parathyroid glands after total thyroidectomy, reduces the incidence of permanent hypoparathyroidism.[1–3,10,11] This procedure is becoming increasingly popular throughout the world. In fact, there is even a method in which all of the parathyroid glands are autotransplanted before total thyroidectomy with no attempt to preserve the in situ blood supply.[12] However, the majority of these reports classify postoperative parathyroid function as being a reduction of transient and/or permanent hypoparathyroidism, and not as a percentage of preoperative recovery.[1–7] Our technique of performing total thyroidectomy to prevent postoperative hypoparathyroidism combines the preservation of parathyroid glands in situ with the autotransplantation of resected or devascularized parathyroid glands. The present study investigates the degree of recovery of parathyroid function following total thyroidectomy employing the above two techniques. Parathyroid function was measured using biochemical and specific endocrine assessments.

Patients and Methods

Patients

Between 1990 and 1997, a total of 426 patients underwent thyroid resection at the Second Department of Surgery of Kagawa Medical University. The subjects of the present study included only 92 of these patients without preoperative hyper- or hypoparathyroidism who underwent total thyroidectomy, consisting of 16 men and 76 women ranging in age from 15 to 84 years, with a mean age of 45.6 ± 17.3 years. The preoperative diagnoses were papillary carcinoma in 72 patients, follicular carcinoma in 10, multiple endocrine neoplasia

type 2A (MEN-2A) in 5, type 2B (MEN-2B) in 1, and Graves' disease in 4. All patients with papillary or follicular carcinoma had bilateral and multiple lesions, or lesions spread in the contralateral thyroid lobe. Furthermore, patients with distant metastases underwent total thyroidectomy for postoperative isotope therapy. All six patients with MEN had bilateral and multifocal carcinoma, while all of those with Graves' disease underwent total thyroidectomy to reduce Graves' ophthalmopathy. Initial total thyroidectomy was performed in 76 patients, and completion thyroidectomy was performed in 16 patients. Unilateral or bilateral lymph node dissection was also performed in the patients with malignant disease.

Methods

During the total thyroidectomy procedure, every attempt was made to identify and carefully preserve each parathyroid gland and its blood supply according to the method of Thompson et al.[13] We also tried to preserve the posterior branch of the superior thyroid artery. If it was necessary to devascularize or separate the parathyroid gland from its surrounding structures, it was autotransplanted into the contralateral sternocleidomastoid muscle or the pectoralis major muscle, using the well-described fine mincing method.[1–3,10–12] The resected parathyroid glands were mince-sliced and implanted within 3–5 min. Parathyroid glands were identified intraoperatively with the naked eye, and any glands suspected of having cancer invasion or metastatic disease were excluded. Final confirmation was obtained by microscopic evaluation of a small graft postoperatively. In our study, the rate of accuracy by naked eye identification was 98.2%. Lipid and thymic tissues mistaken for parathyroid glands were excluded, as were five supernumerary parathyroid glands identified in the dissected lymph nodes.

Patients who suffered both a fall in serum calcium (Ca) to below 8 mg/dl and signs of hypocalcemia, such as tetany, were administered oral 1,25-dihydroxycholecalciferol, 0.5–1.0 μg/day, and oral calcium lactate, 1–2 g/day. Serum Ca and serum intact parathyroid hormone (I-PTH) levels were measured on postoperative day (POD) 1, 7, 14, 30, 90, 180, and 360. Serum Ca levels were corrected by an albumin concentration, the normal range being 8.2–10.2 mg/dl.[14] The level of I-PTH was determined by immunoradiometric assay (Allegro Intact PTH; Nichols Institute Diagnostics, USA), the detection limit being 2 pg/ml, and the normal range being 15–50 pg/ml. Functional recovery of the parathyroid glands was quantified as the ratio of the postoperative I-PTH levels to the preoperative I-PTH levels. Patients were considered to have permanent hypoparathyroidism if 12 months post-operatively they still required daily doses of 1,25-dihydroxycholecalciferol or calcium lactate and their I-PTH levels were below the normal range. The patients were divided into two groups, namely a preservation group, comprising those with one or more parathyroid glands preserved in situ and any autotransplanted glands, and an autotransplantation group, comprising those with only autotransplanted parathyroid glands.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD). Data were analyzed by Fisher's exact probability test or the unpaired *t*-test, and differences were regarded as significant when the P value was less than 0.05.

Results

The preservation group had a mean number of 1.7 ± 0.8 preserved parathyroid glands. A combination of preservation and autotransplantation was performed in 68 patients (82%) from this group, with a mean number of 1.5 ± 1.0 autotransplanted parathyroid glands. The autotransplantation group had a mean number of 2.6 ± 0.9 autotransplanted glands, with a range of two to four glands (Table 1).

Permanent hypoparathyroidism was encountered in 4 of the total of 92 patients (4.3%), being 1 of 83 patients (1.2%) in the preservation group, and 3 of 9 patients (33.3%) in the autotransplantation group. The incidence of permanent hypoparathyroidism in the autotransplantation group was significantly higher than that in the preservation group ($P < 0.01$) (Table 1). The number of parathyroid glands preserved in situ and autotransplanted were significantly higher in the patients who underwent initial total thyroidectomy than in those who underwent completion thyroidectomy ($P < 0.05$); however, the incidence of permanent hypoparathyroidism did not differ significantly between these two groups (Table 2).

The changes in corrected serum Ca levels in 88 patients, excluding the four patients with permanent hypoparathyroidism, are shown in Fig. 1. In the preservation group, the corrected Ca level fell to 8.1 ± 0.3 mg/dl on POD 1, then recovered rapidly to preoperative levels by POD 7. In the autotransplantation group, the corrected serum Ca level fell to 7.2 ± 0.4 mg/dl on POD 1, then recovered gradually to settle at a level lower than the normal range by POD 30. Thereafter, from POD 30 to POD 360, the corrected serum Ca levels remained relatively constant in both groups; however, by POD 360, that of the autotransplantation group was significantly

Table 1. Comparison between the preservation group and the autotransplantation group

	No. of glands preserved	No. of glands transplanted	Permanent hypoparathyroidism No. of patients (%)
Preservation group	1.7 ± 0.8	1.5 ± 1.0	1/83 (1.2%) ⎤**
Autotransplantation group transplanted	0	2.6 ± 0.9	3/9 (33.3%) ⎦
2 glands	0	2	2/4 (50.0%)
3 glands	0	3	1/4 (25.0%)
4 glands	0	4	0/1 (0%)

Values are expressed as means ± SD. ** $P < 0.01$

Table 2. Comparison between initial total thyroidectomy and completion thyroidectomy

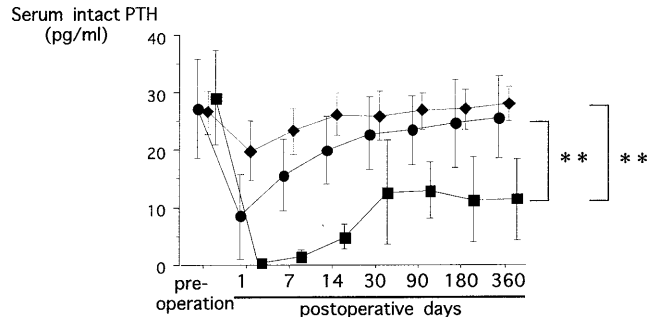|	No. of glands preserved	No. of glands transplanted	Permanent hypoparathyroidism No. of patients (%)
Initial total thyroidectomy	1.6 ± 0.9 ⎤	1.7 ± 1.0 ⎤	2/76 (2.6%) ⎤ $P = 0.08$
Completion thyroidectomy	1.1 ± 0.9 ⎦*	1.1 ± 0.9 ⎦*	2/16 (12.5%) ⎦

Values are expressed as means ± SD. * $P < 0.05$
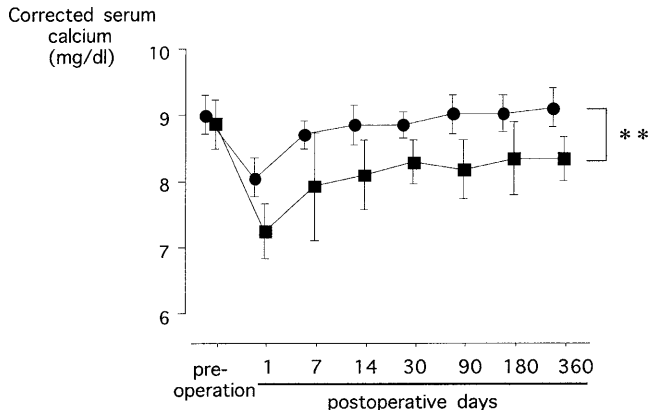
Fig. 1. The changes in corrected serum calcium levels in the preservation group (*circles*) and autotransplantation group (*squares*). The recovery ratio of the calcium value on postoperative day (POD) 360 to the preoperative level between the two groups was statistically significant (** $P < 0.01$)

Fig. 2. The changes in serum intact parathyroid hormone (*PTH*) levels among patients in the preservation and autotransplantation (*squares*; $n = 9$), groups. The preservation group was further divided into subset A (*circles*; $n = 73$), having one or two preserved glands, and subset B (*diamonds*; $n = 10$), having three or four preserved glands. The recovery ratio of intact PTH levels on POD 360 to the preoperative level was significantly lower in the autotransplantation group (** $P < 0.01$)

lower than that of the preservation group ($P < 0.01$) (Fig. 1).

The changes in serum I-PTH levels in the preservation group and the autotransplantation group are shown in Fig. 2. For this analysis, the preservation group was divided into two subsets: group A, consisting of one or two preserved in situ glands; and group B, consisting of three or four preserved in situ glands. In the autotransplantation group, the serum I-PTH levels on POD 1 fell below the detectable limit, then climbed steadily between PODs 7 and 30, and leveled off from POD 30 to POD 360 to a recovery level of 43% of the preoperative

Table 3. Classification of patients in the preservation group according to the serum levels of intact parathyroid hormone on postoperative day 1

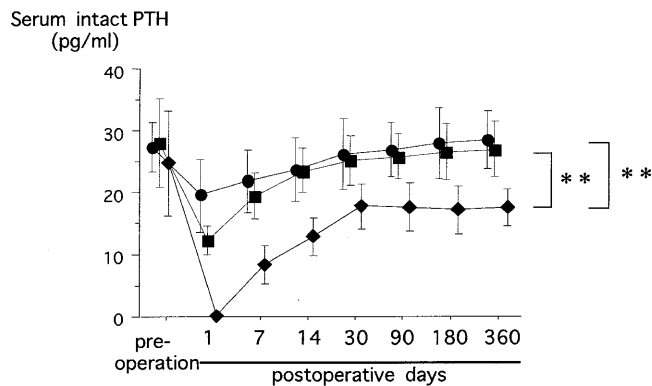| No. of glands preserved	Group I	Group II	Group III
Group A			
1 gland ($n = 43$)	9 (20.9%)	24 (55.8%)	10 (23.3%)
2 glands ($n = 30$)	13 (43.3%)	13 (43.3%)	4 (13.3%)
Group B			
3 glands ($n = 6$)	6 (100%)	0 (0%)	0 (0%)
4 glands ($n = 4$)	4 (100%)	0 (0%)	0 (0%)

Patients whose serum levels of intact parathyroid hormone on postoperative day 1 were within the normal range (group I); detectable and lower than the normal range (group II); and below the detectable limit (group III)

Fig. 3. The pattern of recovery of serum intact PTH levels among the three subgroups with one or two parathyroid glands preseved in situ. *Circles*, group I ($n = 22$); *squares*, group II ($n = 37$); *diamonds*, group III ($n = 14$). The recovery ratio of intact PTH levels on POD 360 to the preoperative level was significantly lower in group III than that in groups I or II (**$P < 0.01$)

values. In the preservation group, subset group A showed a much more marked drop-off in serum I-PTH on POD 1 than subset group B. In fact, the serum levels were almost undetectable in some of the group A patients on POD 1. Subset group B showed a decrease in serum I-PTH on POD 1 to within normal levels, then rapid recovery to the preoperative levels. Subset group A showed rapid recovery after POD 1, and reached serum I-PTH levels similar to those in subset group B. The POD 360 ratio of postoperative I-PTH to preoperative I-PTH was significantly lower in the autotransplantation group than that in either subset of the preservation group ($P < 0.01$) (Fig. 2).

Table 3 takes the subset group A with 1 or 2 preserved glands ($n = 73$) and the subset group B with 3 or 4 preserved glands ($n = 10$) from the preservation group and divides it further into groups I, II, and III, based on the serum levels of intact PTH on POD 1. On POD 1, the serum levels in group I were within the normal range, those in group II were detectable and lower than the normal range, and those in group III were below the detectable limit. It can be seen that all the patients in subset group B fell within group I, having a serum level within the normal range on POD 1. Conversely, the patients in subset group A fell within groups I ($n = 22$), II ($n = 37$), and III ($n = 14$). Figure 3 shows the recovery of serum I-PTH levels in the subset group A patients, plotted by groups I, II, and III. It can be seen that the groups I and II serum I-PTH levels recovered to the preoperative values, while the group III levels, which were undetectable on POD 1, only recovered to 70% of the preoperative values. The levels in group III were significantly lower than those in groups I and II ($P < 0.01$).

Discussion

Postoperative hypoparathyroidism is a common iatrogenic complication following total thyroidectomy.

When a total thyroidectomy is performed, it is difficult to preserve the parathyroid glands in situ with an adequate blood supply, which is why the incidence of postoperative hypoparathyroidism after total thyroidectomy ranges from 1% to 30%.[1–7] This complication is the result of inadvertent removal of the parathyroids, ligation of the blood supply, or secondary destruction due to capsular hematoma.[10]

Patients with latent hypoparathyroidism are usually able to maintain normocalcemia without supplementary therapy, unless the absorption of calcium from the gastrointestinal tract is decreased.[8,15] The incidence of latent hypoparathyroidism based on an incomplete recovery of function is much higher than that of permanent hypoparathyroidism. In fact, Salander and Tisell[8] reported latent hypoparathyroidism in 61% of patients after thyroid surgery when they underwent a calcium deprivation test.

The methods employed for preserving parathyroid function after thyroidectomy are in situ preservation and autotransplantation of the parathyroid glands. Autotransplantation of the parathyroid gland is a simpler method of reducing the incidence of postoperative hypoparathyroidism, but its success is highly dependent on the number of glands transplanted, with one or two glands usually not supplying enough tissue volume to adequately achieve recovery of parathyroid function.[12,16,17] Funahashi et al.[12] investigated the recovery of autotransplanted parathyroid glands by measuring I-PTH levels, and reported that recovery started on POD 7 and leveled off by POD 14; however, even when four parathyroid glands were transplanted, the I-PTH recovery was only 80% of the preoperative level by POD 28. According to their results of long-term follow-up for a

mean period of 34 months, the I-PTH levels from 1 month to several years postoperatively remained relatively constant, but did not recover to preoperative levels.[18] In our study, the mean 1-year postoperative recovery for the autotransplantation group was 43% of the preoperative levels, while that for four transplanted glands was 70% of the preoperative I-PTH levels. These results imply that parathyroid gland activity cannot be expected to recover to the preoperative levels in patients who undergo autotransplantation only. On the other hand, the preoperative levels of I-PTH recovered in over 80% of patients (69/83) in whom at least one parathyroid gland was preserved in situ with an intact blood supply. Therefore, whenever feasible, parathyroid glands should be preserved in situ and this technique must be mastered by every thyroid surgeon.

Concerning parathyroid anatomy, it is generally accepted that there are four parathyroid glands, each of which has a single end artery that arises from the inferior thyroid artery. In addition, the superior thyroid artery and/or a distinct anastomosing branch between the superior and inferior thyroid arteries supplies the upper parathyroid glands in many patients.[19] Therefore, not only the branches of the inferior thyroid artery, but also the posterior branch of the superior thyroid artery should be preserved to supply the upper parathyroid glands. We have followed this technique, in addition to the method of Thompson et al.,[13] to preserve the parathyroid glands in situ.

I-PTH has a very short biologic half-life and its activity is a suitable index of parathyroid gland function.[20–23] We found that if the I-PTH levels in patients whose parathyroid glands were preserved in situ were higher than detectable limits on POD 1, the parathyroid function recovered almost completely to the preoperative levels; however, if they were below detectable limits, the parathyroid function did not recover sufficiently by 1 year postoperatively. Even in this subset of patients with preserved in situ parathyroid glands, the level of I-PTH recovered significantly by POD 7 compared with the autotransplantation-only group in which levels of I-PTH were just becoming detectable by POD 7. The reason that the I-PTH levels in this subset of patients with preserved in situ parathyroid glands did not recover sufficiently might be attributed to the possibility that the blood supply was partially inhibited by blood congestion and hematoma, which indicates the necessity to preserve as many parathyroid glands in situ as possible, to compensate for suboptimally functioning glands.

In conclusion, our findings suggest that parathyroid glands should be preserved in situ whenever feasible, to promote better recovery of postoperative function, and that the I-PTH level on POD 1 in patients in whom parathyroid glands have been preserved in situ may be a good parameter for predicting the degree of long-term postoperative functional recovery.

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