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The inferior parathyroid glands preserved in site recover faster than the superior parathyroid glands preserved in site after thyroid surgery for carcinoma

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Abstract

Due to the great difficulty in being preserved in site for the variable positions, the inferior parathyroid glands were advised to being routinely autotransplanted to prevent permanent hypoparathyroidism. The aim of this study was to compare the performance in the function of the superior parathyroid glands preserved in site with that of the inferior parathyroid glands preserved in site.

We conducted a retrospective study including patients who underwent thyroid surgery for papillary thyroid carcinoma at our department between January 2014 and June 2018. According to the number and original position of the autoplastic parathyroid gland(s), patients were divided into group 1 (1 superior parathyroid gland), group 2 (1 inferior parathyroid glands), group 3 (1 superior parathyroid gland and 1 inferior parathyroid gland) and group 4 (2 inferior parathyroid glands). The postoperative complications and serum parathyroid hormone and calcium were analyzed.

A total of 368 patients were included in the study, among them 27, 243, 40, and 58 patients were divided into group 1, group 2, group 3, and group 4, respectively. Compared with those in group 2, the serum parathyroid hormones were higher at 1 week (2.98 ± 1.52 vs 2.42 ± 0.89, $P = .049$) and 2 weeks (3.49 ± 1.42 vs 2.8 ± 0.81, $P = .019$) postoperatively in group 1. There was also significantly different in the serum parathyroid hormone at 2 weeks postoperatively between group 3 and group 4 (2.95 ± 0.98 vs 2.58 ± 0.82, $P = .047$).

The inferior parathyroid glands preserved in site recover faster than the superior parathyroid glands preserved in site.

Abbreviations: BCND = bilateral central neck lymph node dissection, BLND = bilateral neck lymph node dissection, BMI = body mass index, F = female, LND = lateral neck lymph node dissection (compartments II–V), LT = lobe thyroidectomy, M = male, PG = parathyroid gland, Post = postoperative, Pre = preoperative, TT = total thyroidectomy, UCND = unilateral central neck lymph node dissection, ULND = unilateral neck lymph node dissection.

Keywords: autotransplantation, carcinoma, parathyroid gland, position, thyroid

1. Introduction

Postoperative hypoparathyroidism has being one of the most common complications after thyroid surgery.[1,2] It was the best way to protect the function of the parathyroid gland (PG) that preserving all the PGs in site.[3,4] Although the strategies of preserving the PGs in site have improved in recent decades, such as loupes, marking instruments (carbon nanoparticles, near-infrared imaging and $Tc99^{m}$-sestaMIBI), and meticulous dissection, it is still full of challenges for thyroid surgeons to preserve all the PGs in site.[5–11] PG autotransplantation was the exclusive way to save the function of the PGs that could not be preserved in site.[12]

It is no doubt that the PGs that were successfully autotransplanted could be able to contribute function to the overall

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BW and C-RZ contributed equally to this study and should be treated as co-first authors.

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function of the PGs.[13,14] However, due to the destruction of blood supply, it always took at least 4 weeks for the autoplastic PGs to recover function.[15–17] During this time, the PGs in site were the primary functional parenchyma. Because of the potential injury from mechanical or thermal trauma, hematoma formation, or/and partial devascularization, the PGs in site might not be able to function fully.[18,19] Some research confirmed that even if all the PGs were preserved in site, permanent hypoparathyroidism might occur.[17,20]

In consideration of the predictable function of the autoplastic PGs, the uncertain function of the PGs preserved in site, and the variable location of the inferior PGs, some researchers advocated routine inferior PGs autotransplantation to decrease the incidence of postoperative permanent hypoparathyroidism.[17,20–22] While the function of the PGs preserved in site needed to be evaluated. Therefore, we conducted this study to compare the performance in the function of the superior parathyroid glands preserved in site with that of the inferior parathyroid glands preserved in site.

2. Methods

2.1. Patients

We conducted the retrospective study including patients who underwent thyroid surgery for papillary thyroid carcinoma at the Department of Thyroid and Breast Surgery of The Third People's Hospital of Chengdu between January 2014 and June 2018. We excluded these patients:

1. patients whose data could not be collected completely;
2. patients who had undergone thyroid surgery or neck surgery;
3. patients who were suffering from parathyroid disease;
4. patients whose surgical extent was less than total thyroidectomy (TT) with bilateral central neck lymph node dissection (BCND);
5. patients who underwent inadvertently removed PG(s);
6. patients who underwent autotransplantation of 0, 3, or 4 PGs.

These patients with 1 or 2 autoplastic PGs were included and analyzed. And according to the original position of the autoplastic PG, the patients with 1 autoplastic PG were divided into group 1 (1 autoplastic superior PG) and group 2 (1 autoplastic inferior PG), and the patients with 2 autoplastic PGs were divided into group 3 (1 autoplastic superior PG and 1 autoplastic inferior PG) and group 4 (2 autoplastic inferior PGs). Informed consent was got from these patients and the study was approved by the medical ethics committee of The Third People's Hospital of Chengdu.

2.2. Perioperative management

A standardized perioperative management program was implemented for patients. Preoperative assessment including neck ultrasound, laryngoscopy, thyroid function, serum parathyroid hormone (PTH), and calcium. When the tumor was suspicious for the advanced stage according to the physical examination and aforementioned assessments, neck computerized tomography was used. Serum PTH and calcium were measured at 1day, 3 days, 1 week, 2 weeks, 1month, 3 months, 6 months, and 12 months postoperatively. When patients suffered from symptomatic hypocalcemia, such as acroanesthesia, paresthesia, and spasm of facial muscles, they were prescribed with oral and/or intravenous calcium supplementation. The postoperative hypoparathyroidism and hypocalcemia were defined as the level of serum PTH and calcium were less than the normal limit (range: PTH, 1.6–6.9 pmol/L; calcium, 2.1–2.7 mmol/L), respectively. Postoperative immediate, protracted and permanent hypoparathyroidism and hypocalcemia were defined as that hypoparathyroidism and hypocalcemia occurred at 1 day, 1 month, and 6 months postoperatively, respectively.

2.3. Surgical procedures and the method of PG autotransplantation

Two professional thyroid surgeons (Wu J and Yao X) performed the same surgical procedures as the descriptions from Su et al.[23] Meticulous capsule dissection was the routine method to protect the PGs, and this surgical technique was defined as that the third-tier blood vessels to and from the thyroid should be treated close to the natural thyroid capsule during thyroid resection.[9] During surgery, every specimen would be examined carefully to avoid to inadvertently remove PG. As for the PGs that were non-viable or found in the intraoperative specimens, they would be transplanted in the sternocleidomastoid muscle after confirmation by intraoperative frozen biopsy. The method of PG autotransplantation was that the PG was fragmented into 1-mm pieces and inserted into 3 to 4 muscular pockets. When the pathologists discovered parathyroid tissue in the postoperative paraffin specimens, the tissue was regarded as the inadvertently excisional PG.

2.4. Data collection

The demographic characteristics, preoperative assessments, surgical extent, original location and number of the autoplastic and inadvertently excisional PG(s), tumor characteristics, serum PTH and calcium, and postoperative complications were collected.

2.5. Statistical analysis

The statistical analyses were performed with SPSS version 23.0 software (SPSS Inc, Chicago, IL). Continuous data and categorical characteristics were expressed as mean ± standard deviation (SD) and absolute numbers, respectively. Student *t* test or the Mann–Whitney test were used for the analyses of continuous variables, and Pearson Chi-Squared test or Fisher exact test was used for the analyses of categorical variables. Statistical significance was set at $P < .05$.

3. Results

As shown in Figure 1, a total of 1013 patients received thyroid surgery in our department during this time and were reviewed. Among these patients, 368 patients met the inclusion criteria and were included in the analysis. Two hundred seventy patients underwent 1 PG autotransplantation, among them 27 patients accepted the superior PG autotransplantation (group 1) and 243 patients accepted the inferior PG autotransplantation (group 2). Autotransplantation of 2 PGs was performed in 98 patients, of them 40 patients underwent autotransplantation of 1 superior PG and 1 inferior PG (group 3), and 58 patients underwent autotransplantation of 2 inferior PGs (group 4), and no patients underwent autotransplantation of 2 superior PGs. It happened to

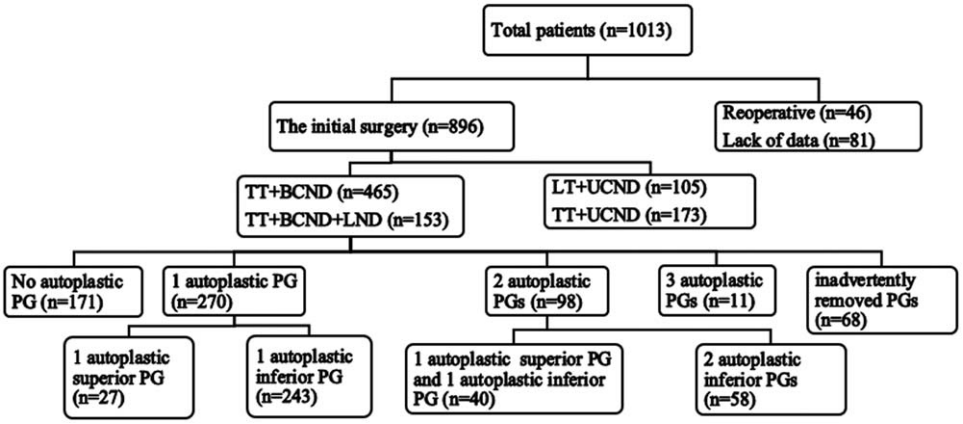

Figure 1. Flow chart of screening patients. BCND = bilateral central neck lymph node dissection, LND = lateral neck lymph node dissection, LT = lobe thyroidectomy, PG = parathyroid gland, TT = total thyroidectomy, UCND = unilateral central neck lymph node dissection.

11 patients that 3 PGs were autotransplanted. And no patients underwent autotransplantation of 4 PGs.

Table 1 showed the characteristics of patients and tumors among the 4 groups. There were no significant differences in gender, age, body mass index (BMI), comorbidities (hypertension, diabetes, thyroiditis, Graves disease, hypothyroidism, and nodular goiter), preoperative lymphadenectasis in central zone, the largest size of intumescent lymph nodes, use of carbon nanoparticles, surgical extent, bilateral lobe of tumors, multifocality of tumors, gross extrathyroidal extension, size of the largest tumor, tumor location, number of lymph nodes harvested in the central zone, number of metastatic lymph nodes in the

Table 1

The characteristics of patients and tumors among the 4 groups.

Variables	One autoplastic PG			Two autoplastic PGs		
	group 1 (n=27)	group 2 (n=243)	*P*	group 3 (n=40)	goup 4 (n=58)	*P*
Gender (F/M)	19/8	168/75	.9	29/11	39/19	.58
Age (years)	39.3±12.1	41.3±12.3	.43	42.1±12.3	43.1±13	.69
BMI (kg/m^2)	22.7±3	23.5±3.4	.28	22.8±3.7	23.1±3.1	.66
Hypertension	2	28	.75	8	4	.07
Diabetes	1	5	.47	1	1	>.99
Hyperthyroidism	0	8	>.99	0	2	.51
Hypothyroidism	1	2	.27	0	1	>.99
Hashimotos Thyroiditis	9	76	.83	10	18	.52
Nodular goiter	12	142	.16	13	21	.71
Preoperative lymphadenectasis in central zone	10	73	.46	21	22	.18
Largest size of lymph nodes (mm)	12.7±4.4	12.3±4.6	.78	13.8±6.8	13.1±6.2	.72
Carbon nanoparticles	26	223	.71	37	51	.52
Surgical extent			.54			.42
TT+BCND	18	184		25	43	
TT+BCND+ULND	7	49		13	12	
TT+BCND+BLND	2	10		2	3	
Bilateral lobe tumors	10	67	.3	11	17	.8
Multifocal tumors	11	78	.37	12	19	.77
Gross extrathyroidal extension	5	47	.92	13	11	.13
Largest tumor size (mm)	13.5±6.9	16.1±10.2	.19	17.2±10.4	17.4±11.8	.91
Tumor location (upper/middle/lower/isthmus)	8/14/4/1	70/99/59/15	.59	5/22/8/5	15/23/12/8	.35
Number of lymph nodes in the central zone	12.9±5	14.1±6.9	.37	13.1±7.4	15.6±7.3	.09
≤10	8	77	.83	17	16	.13
>10	19	166		23	42	
Number of metastatic lymph nodes in the central zone	4±4.3	4.3±4.9	.8	4.8±5.2	4.1±4.2	.45
≤5	17	167	.54	26	41	.55
>5	10	76		14	17	
Pathological T classification (pT1∼T2/pT3∼T4)	22/5	191/52	.48	26/14	45/13	.2
Pathological N classification (pN0/pN1)	8/19	57/186	.73	6/34	15/43	.17
AJCC stage (I∼II/III∼IV)	27/0	237/6	>.99	39/1	58/0	.41
Postoperative length of stay (days)	4.5±2	5±3.1	.44	5.2±2.3	6.3±7.4	.39

BCND = bilateral central neck lymph node dissection, BLND = bilateral neck lymph node dissection (compartments II–V), BMI = body mass index, F = female, M = male, PG = parathyroid gland, TT = total thyroidectomy, ULND = unilateral neck lymph node dissection (compartments II–V).

Table 2

The postoperative complications among the 4 groups.

Variables	One autoplastic PG			Two autoplastic PGs		
	group 1 (n=27)	group 2 (n=243)	*P*	group 3 (n=40)	goup 4 (n=58)	*P*
Postoperative immediate hypoparathyroidism (%)	14 (51.9)	123 (50.7)	.9	23 (57.5)	39 (67.2)	.33
Protracted hypoparathyroidism (%)	2 (7.4)	16 (6.6)	.7	1 (2.5)	2 (3.4)	>.99
Permanent hypoparathyroidism (%)	1 (3.7)	4 (1.6)	.41	0 (0)	1 (1.7)	>.99
Postoperative immediate hypocalcemia (%)	16 (59.3)	107 (44.0)	.13	19 (47.5)	31 (53.4)	.56
Protracted hypocalcemia (%)	2 (7.4)	22 (9.1)	>.99	0 (0)	2 (3.4)	.51
Permanent hypocalcemia (%)	1 (3.7)	9 (3.7)	>.99	0 (0)	2 (3.4)	.51
Transient hoarseness (%)	0 (0)	8 (3.3)	>.99	2 (5)	3 (5.2)	>.99
Postoperative bleeding (%)	1 (3.7)	4 (1.6)	.41	1 (2.5)	0 (0)	.41
Chylous fistula (%)	0 (0)	2 (8.2)	>.99	0 (0)	3 (5.2)	.27
Pneumonia (%)	0 (0)	6 (2.5)	>.99	1 (2.5)	3 (5.2)	.64

PG = parathyroid gland.

central zone, pathological T classification, pathological N classification, AJCC stage, postoperative length of stay between group 1 and group 2, nor were there significant differences in these characteristics of patients and tumors between group 3 and group 4.

As for the postoperative complications, the incidences of postoperative immediate, protracted, and permanent hypoparathyroidism were 54.1%, 5.7%, and 1.6% in the study, 50.7%, 6.7%, and 1.9% in the group of patients with 1 autoplastic PG, 63.3%, 3.1%, and 1.0% in the group of patients with 2 autoplastic PGs, respectively. But there were no significant differences in the incidences of postoperative immediate, protracted, and permanent hypoparathyroidism between group 1 and group 2, between group 3 and group 4. No significant differences were observed in the incidences of postoperative transient hoarseness, bleeding, and pneumonia between group 1 and group 2, nor were they observed in the incidences of these complications between group 3 and group 4 (Table 2).

The changes in serum PTH were shown in Figure 2. The serum PTHs fell obviously at 1 day postoperatively, then climbed steadily within 1 month postoperatively. Compared with those in group 2, the serum PTHs were higher at 1 week (2.98 ± 1.52 vs 2.42 ± 0.89, $P = .049$) and 2 weeks (3.49 ± 1.42 vs 2.8 ± 0.81, $P = .019$) postoperatively in group 1 (Fig. 2A). There was also significantly different in the serum PTH at 2 weeks postoperatively between group 3 and group 4 (2.95 ± 0.98 vs 2.58 ± 0.82, $P = .047$; Fig. 2B).

4. Discussion

Researchers have reached the consensus that PG autotransplantation will increase the risk of postoperative transient hypoparathyroidism during thyroid surgery.[24,25] But there is a controversy over the relationship between PG autotransplantation and permanent hypoparathyroidism.[20,25,26] Several studies revealed the autoplastic PG could not recover fully,[3,4,27] whereas some studies suggested PG autotransplantation did not affect the incidence of permanent hypoparathyroidism.[25,28] And some studies even indicated that it would decrease the incidence.[20,22] What is more, studies further showed the number of autoplastic PGs was related to the incidence of permanent hypoparathyroidism.[16,17,22,29] In view of the variable location, the inferior PGs were regarded as the more suitable PGs for transplantation than the superior PGs.[17,22] Then, the present study was conducted to evaluate whether the superior PGs or the inferior PGs were more suitable for being preserved in site in terms of function.

Previous researches reported that the incidence of transient hypoparathyroidism varied from 27.7% to 60%, and the incidence of permanent hypoparathyroidism was 4.6% to

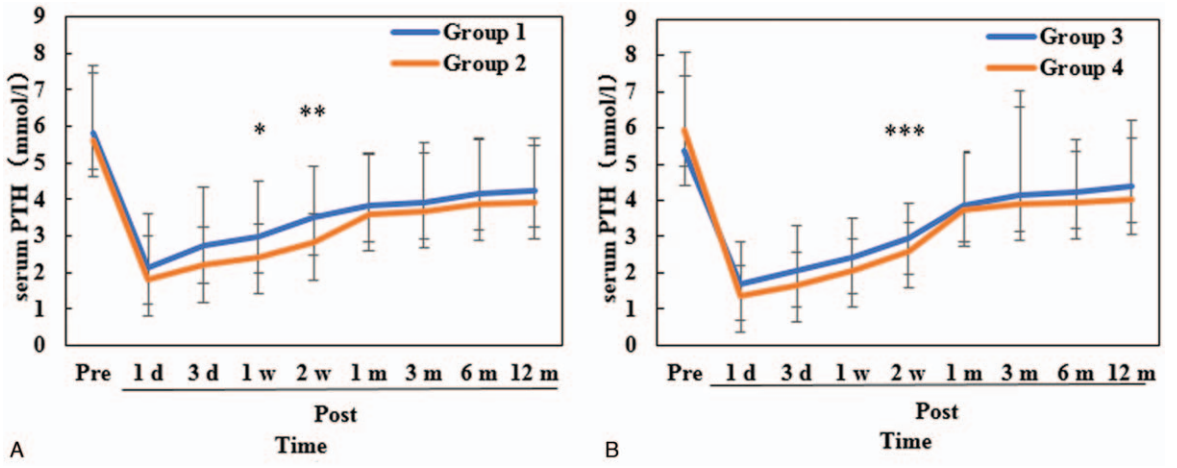

Figure 2. Changes of the serum parathyroid hormone. PTH = parathyroid hormone, Pre = preoperative, Post = postoperative, $^{*}P = .049$, $^{**}P = .019$, $^{***}P = .047$.

16.2%.[1,2] In the present study, the incidences of hypoparathyroidism were in accordance with them (postoperative immediate hypoparathyroidism, 54.1%; permanent hypoparathyroidism 1.6%). Researches also confirmed that the incidence of transient hypoparathyroidism was positively correlated with the number of the autoplastic PGs.[18,20,24] A similar result was obtained in this study that the incidence of transient hypoparathyroidism in the patients with 2 autoplastic PGs was higher than that in the patients with 1 autoplastic PG (63.3% vs 50.7%, $P = .033$). This phenomenon might be attributed to the reduction in functional parathyroid parenchyma. The reason for approximate incidences of transient hypoparathyroidism between group 1 and group 2, between group 3 and group 4, was that the number of the functional PGs was same at this time.

Ponce de Leon-Ballesteros and his colleagues discovered that 3 or more PGs should be preserved in site to decrease the risk of permanent hypoparathyroidism.[30] And de Jong et al and Lorente-Poch et al believed that the more the PGs were preserved in site, the lower the incidence of permanent hypoparathyroidism was.[31,32] However, several other studies suggested that autotransplantation of 2 or more PGs could prevent permanent hypoparathyroidism.[16,17] There were no significant differences in the incidences of permanent hypoparathyroidism between the patients with 1 autoplastic PG and the patients with 2 autoplastic PGs in the present study (1.9% vs 1.0%, $P > .99$). And we also obtained the same results as the preceding result when comparing group 1 with group 2 and comparing group 3 with group 4. The fact that the number of the functional PGs, no matter they were preserved in site or transplanted, was same might be responsible for these outcomes. The group of patients with fewer PGs preserved in site included patients with inadvertently removed PG (s) in these researches conducted by Ponce de Leon-Ballesteros et al, de Jong et al, and Lorente-Poch et al. Another reason might be that the sample size was small.

The inferior PGs originated from the third pharyngeal pouch and underwent a long way of descent, which led to the variable location and the great difficulty in being preserved in site.[33,34] Teshima and his colleagues believed that the inferior PGs should be autotransplanted to prevent permanent hypoparathyroidism.[17] In the present study, the number of patients in group 2 and group 4, where the patients underwent more inferior PG autotransplantations, was larger than that in group 1 and group 3. Whereas, there were no significant differences in characteristics of patients and tumors between group 1 and group 2, between group 3 and group 4, which meant it was the inferior PGs own characteristics that led to transplantation.

Some strategies which were based on the PGs themselves have been proposed to protect their function.[26,35,36] Su et al created a new classification of PGs based on the positional relationship among PGs, thyroid gland, and thymus to guide whether PGs should be preserved in site or autotransplanted.[26] Cui and coworkers classified the PGs according to the positional and blood supply relationship between the PGs and the thyroid gland and determined whether the PGs should be autotransplanted or preserved in site by observing the changes of color in PGs during surgery.[36] Lee and colleagues introduced a technique for preserving the inferior thyroid vein and confirmed this technique was helpful for reducing postoperative hypocalcemia and promoting recovery.[35] Pasta et al traced the PGs with $Tc99^m$-sestaMIBI after inhibiting the interference of $Tc99^m$-sestaMIBI uptake of the thyroid gland by means of the administration of Lugol solution.[11] In this study, whether or not the PGs were autotransplanted was decided by the chief surgeon who took into consideration the experience, anatomy, and changes of color in PGs.

Although there were no significant difference in the incidences of postoperative immediate, protract and permanent hypoparathyroidism between group 1 and group 2, between group 3 and group 4, the serum PTHs were higher in group 1 at 1 week postoperatively, and in group 1 and group 3 at 2 weeks postoperatively. This phenomenon implied a faster recovery of parathyroid function in these group. Burger et al discovered that the blood supply of 67.5% to 89.5% of the superior PGs and 81.4% to 93.7% of the inferior PGs was associated with the inferior thyroid artery and thyroid ima artery.[37] The long way of the branches from the inferior artery or thyroid ima artery to the superior PGs might increase the risk of injury, which resulted in a slower functional recovery of the superior PGs preserved in site. El-Sharaky et al confirmed that it took 2 weeks for the autoplastic PGs to restart to function and 4 weeks to regain function.[16] That might be the reason why the incidence of protracted hypoparathyroidism was not affected by the original location of autoplastic PGs.

5. Conclusion

In summary, we could come to the conclusions that the inferior PGs preserved in site recover faster than the superior PGs preserved in site, and that the original positions of the autoplastic PGs do not affect the incidences of postoperative immediate, protracted and permanent hypoparathyroidism, and that the inferior PGs were not the more suitable choice for routine autotransplantation than the superior PGs in terms of function unless they could not be able to be preserved in site.

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