

# Study on Rapid Intraoperative Parathyroid Hormone to Identify and Protect Parathyroid Gland during Total Thyroidectomy

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**Abstract: Objective:** By comparison and analysis preoperative and postoperative related indicators of the Control group (group A) and Fine-needle aspiration(FNA) rapid intraoperative parathyroid hormone (rIO-PTH) group (group B) .To further explore whether rIO-PTH has a certain value for the intraoperative identification and protection of the parathyroid glands, and reduce the incidence of hypoparathyroidism and hypocalcemia in postoperative. Improve the quality of life of patients with thyroidectomy. **Methods:** In this study, the patients were divided into group A, group B, with 35 cases in each group. In group B, the suspected parathyroid tissues was aspirated by FNA. Parathyroid gland was identified by the concentration of rIO-PTH in the puncture fluid. In group A, only in the traditional thyroid surgery way. Comparative analysis of postoperative PTH and blood calcium, numbers of intraoperative identification of parathyroid glands, the incidence of hypoparathyroidism and hypocalcemia in postoperative. **Results:** During the operation, the parathyroid glands were identified, the average of group A was (2.6±0.3), the average of group B was (3.0±0.2). There was a statistically significant difference in the average number of parathyroid glands between the two groups (P<0.05). Postoperative blood calcium and PTH levels were decreased in all the two groups, and the differences were statistically significant (p < 0.05) on the 1st, 4th, 7th and 30th day after surgery. The incidence of postoperative hypocalcemia was 28.6% (10/35) in group A and 8.6% (3/35) in group B. The incidence of postoperative hypothyroidism was 37.1% (13/35) in group A and 14.3% (5/35) in group B. The incidence of hypocalcemia and hypothyroidism in the two groups was statistically significant difference (P < 0.05). **Conclusion:** Fine-needle aspiration (FNA) rapid intraoperative detection of parathyroid hormone (rIO-PTH) can identify parathyroid tissue. rIO-PTH can significantly reduce the excessive reduction of postoperative blood calcium and PTH levels in patients, and effectively reduce the incidence of postoperative hypocalcemia and hypothyroidism. rIO-PTH has high clinical application value in identifying and protecting parathyroid gland in thyroid surgery.

**Keywords:** Parathyroid Gland, Fine Needle Aspiration, Rapid Intraoperative Parathyroid Hormone, Hypocalcemia, Hypothyroidism

## 1.Introduction

In recent years, with the wide application of thyroid ultrasound in examination, the detection rate of thyroid cancer increases year by year, And the incidence of thyroid cancer is also on the rise, the incidence of women is significantly higher than that of men<sup>[1]</sup>.Thyroid cancer is the most common malignant tumor of thyroid, accounting for about 1% of all malignant tumors. Current drugs and so-called food treatments are ineffective, and surgery is now the preferred treatment. However, the anatomy of the thyroid is complex and the organs are dense. In particular, the location and function of the parathyroid gland are variable, which increases the risk of missection or injury of the parathyroid gland<sup>[2]</sup> .

Hypoparathyroidism (HPT) has become one of the important complications of thyroid surgery. HPT is divided into temporary and permanent<sup>[3]</sup>. HPT may leading to the occurrence of hypocalcemia. Hypocalcemia is clinically manifested as numbness and tingling sensation around the lips and fingertips, hand and foot muscle spasm and facial muscle spasm. Patients need long-term calcium and vitamin D supplements after surgery<sup>[4]</sup>. This postoperative complication seriously affects the postoperative quality of life and brings inconvenience and pain to patients. Therefore, it is important to identify and protect the parathyroid gland during operation. In situ parathyroid protection technology is the most important, simple and widely used parathyroid protection technology at

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present, but it relies too much on the personal experience of the surgeon<sup>[5,6]</sup>. At present, the extensive application of staining technology, endoscopy and fluorescence technology has reduced the damage of parathyroid gland, but there are some deficiencies. Recent reports have stated that rapid intraoperative parathyroid hormone (rIO-PTH) levels from tissue fine needle aspiration (FNA) may identify in parathyroid tissues, and it is a simple and convenient new method<sup>[7,8]</sup>. In this study, rIO-PTH assay of suspected parathyroid tissue was performed using FNA to identify the parathyroids during thyroidectomy, the feasibility of this method is further verified.

## 2. Materials and methods

### 2.1 Patient data

Total thyroidectomy for thyroid diseases admitted to our hospital from August 2017 to February 2018 was selected as the research object, a total of 140 patients, including 51 male patients and 89 female patients, aged from 19 to 75 years old, The average age is (42.93±9.17) years. All patients volunteered to participate in the study and signed the informed consent.

Inclusion criteria: (1) Age over 18 years old; (2) primary thyroid surgery and total thyroidectomy; (3) preoperative examination of serum calcium and Parathyroid hormone (PTH) in the normal range; (4) previous no history of neck surgery, radiotherapy history; (5) the patient information is complete; (6) Laryngoscopy was performed before surgery and the results were normal. Exclusion criteria: (1) previous history of parathyroid gland and neck surgery; (2) preoperative examination of blood calcium and PTH is not in the normal range; (3) patients with liver and kidney dysfunction; (4) using hormones and immunosuppressive agents; (5) combined with other tumor history.

### 2.2 Surgical method

Patients were randomly divided into control group (Group A) and rIO-PTH group (Group B), with 35 cases in each group. Group A included 13 males and 22 females, with an average age of (43.60±8.6) years. Group B included 12 males and 23 females, with an average age of (43.31±9.13) years.

rIO-PTH group (Group B): The skin and anterior cervical fascia were cut open layer by layer, and the

hypohyoid muscle group was separated. When the thyroid gland was detected, the proper thyroid capsule should be protected. The gland should not be turned over for the time being to prevent parathyroid gland injury. Locate the tumor. Open the thyroid capsule, separation of thyroid, according to the anatomical location to find suspicious parathyroid tissue, using needles and 26 1 ml syringe vaccine containing 0.2 ml saline puncture pumping the suspicious tissue, while each piercing suspicious organization for 3 to 5 times in total suction, while maintaining the appropriate negative pressure (Fig. 1 a and B). The sample was diluted with 1ml normal saline and immediately transferred to the laboratory for PTH detection to obtain the concentration of rIO-PTH. If the rIO-PTH range is about 145.2~5000pg/L (chemiluminescence, instrument manufacturer is beckman company, Model dxi-800), it can be confirmed as parathyroid gland. Then continue the thyroid surgery in accordance with the principles of surgery. Control group (Group A): Thyroid surgery was performed according to traditional methods.

### 2.3 Observation item

(1) The age, sex, preoperative parathyroid hormone and serum calcium levels were recorded in the four groups. (2) The levels of serum calcium and parathyroid hormone were measured and recorded on the 1st, 4th, 7th and 30th day after operation in the four groups. (3) The incidence of hypocalcemia and hypoparathyroidism in the four groups were recorded. (4) Record the number of identifying parathyroid glands in each group during operation.

### 2.4 Statistical methods

The values were analyzed by SPSS 22.0 statistical software. The measurement data in accordance with the normal distribution were expressed as mean ± standard deviation ( $\bar{x} \pm s$ ). The mean between the two groups was compared by independent sample t test. One-way analysis of variance was used for comparison.  $P < 0.05$  was considered statistically significant.

## 3. Results

### 3.1 Comparison of general information

There was no significant difference between the two groups in terms of gender and age ( $P > 0.05$ ), which was comparable (table 1).

Table 1 comparison of general data between the two groups

Group	Cases, n	Gender		Age ( $\bar{x} \pm s$ )
		Male	Female	
A	35	13	22	43.60±8.60
B	35	12	23	43.31±9.13
t value ( $\chi^2$ value)			0.062	0.1368
P value			0.803	0.8916

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### 3.2 Intraoperative recognition of parathyroid gland

Parathyroid tissues were found in all groups of patients, and there was no case that the parathyroid glands could not be recognized during operation. A total of 91 parathyroid glands were identified in group A, with an average of (2.6±0.3). A total of 105 parathyroid glands

were identified in group B, with an average of (3.0±0.2). Anova was performed for each group, t=6.5633, P < 0.05, so according to the test results, the overall mean of each group was not equal, and the difference was statistically significant (table 2).

Table 2 comparison of intraoperative parathyroid gland recognition between the two groups

Group	Cases,n	Number of parathyroid glands identified	Mean number of parathyroid glands identified ( $\bar{x}\pm s$ )
A	35	91	2.6±0.3
B	35	105	3.0±0.2
t value			6.5633
P value			0.0000

### 3.3 Preoperative and postoperative changes of serum calcium level were observed in the two groups

After the comparison of preoperative blood calcium levels between the two groups, p > 0.05, the difference was statistically significant and comparable.

Postoperative serum calcium levels were decreased in both groups. Comparison of serum calcium levels between the two groups at the same time points on day 1st, 4th, 7th and 30th after surgery showed a statistically significant difference (p < 0.05) (table 3).

Table 3 changes of serum calcium levels in the two groups before and after surgery ( $\bar{x}\pm s$ )

Group	Cases,n	Blood calcium (mmol/L)				
		preoperative	Day 1st after surgery	Day 4th after surgery	Day 7th after surgery	Day 30th after surgery
A	35	2.38±0.21	2.19±0.19	2.08±0.21	2.11±0.18	2.23±0.20
B	35	2.36±0.20	2.32±0.18	2.30±0.22	2.34±0.20	2.35±0.21
t value		0.4080	2.9385	4.2794	5.0570	2.4480
P value		0.6846	0.0045	0.0001	0.0000	0.0169

### 3.4 Preoperative and postoperative changes of PTH were observed in the two groups

Preoperative parathyroid hormone levels of the two groups were compared, p > 0.05, the difference was statistically significant and comparable. Postoperative

PTH level of patients in both groups decreased, and the PTH level at the same time points of 1st, 4th, 7th and 30th days after surgery was compared between the two groups (p < 0.05), and the difference was statistically significant (table 4).

Table 4 changes of PTH level before and after surgery in the two groups ( $\bar{x}\pm s$ )

Group	Cases,n	PTH (pg/ml)				
		preoperative	Day 1st after surgery	Day 4th after surgery	Day 7th after surgery	Day 30th after surgery
A	35	33.46±5.12	17.05±5.98	18.89±5.78	20.05±6.17	27.16±5.75
B	35	34.58±4.87	24.67±5.82	25.34±5.81	29.01±6.09	31.23±5.98
t value		0.9377	5.4023	4.6561	6.1144	2.9024
P value		0.3517	0.0000	0.0000	0.0000	0.0050

### 3.5 Hypocalcemia and hypoparathyroidism in the two groups after surgery

There was no permanent hypoparathyroidism in each group, but hypocalcemia and temporary hypoparathyroidism occurred in each group. The incidence of postoperative hypocalcemia was 28.6% (10/35) in group A and 8.6% (3/35) in group B. The

incidence of postoperative hypothyroidism was 37.1% (13/35) in group A and 14.3% (5/35) in group B. The incidence of hypocalcemia and hypoparathyroidism in the two groups was significantly higher in group A than in group B, and the difference was statistically significant (P < 0.05). (table 5)

Table 5 analysis of postoperative hypocalcemia and hypoparathyroidism in the two groups ( cases)

Group	Cases,n	hypocalcemia		hypoparathyroidism	
		Yes	No	Yes	No
A	35	10	25	13	22
B	35	3	32	5	30
$\chi^2$ value		4.629		4.786	
P value		0.031		0.029	

#### 4. Discussion

Parathyroid glands (PTG) for small endocrine glands, closely attached on thyroid gland leaves around the back of the thyroid gland leaf of fibrous capsule around inside, can also be hidden within the thyroid parenchyma. The number is not certain, it is 4 commonly, up and down of each side 1. In embryonic development, the parathyroid gland originates from the fourth pharyngeal sac and is attached to the posterior surface of the thyroid gland. The inferior parathyroid gland originates from the third pharyngeal sac and descends with the thymus gland. Therefore, from the perspective of histoembryology, the location of the parathyroid gland is relatively constant, generally located at the junction of the upper and middle 1/3 of the posterior margin of the lateral lobe of the thyroid. However, the location of the inferior parathyroid gland varies greatly and is mostly located near the inferior thyroid artery near the lower end of the posterior margin of the lateral lobe of the thyroid gland. Parathyroid glands may also be located outside the thyroid sheath or embedded in the gland parenchyma. The incidence of ectopic parathyroid is less than 1%, while ectopic parathyroid is most commonly located in the anterior or posterolateral surface of the hypothyroid gland, about 39% of which is located in the thyroid thymus ligament, about 15% in the carotid sheath, and about 2% in the thymus and pericardium<sup>[9, 10]</sup>. 80% of the blood supply of the upper parathyroid gland comes from the ascending branch of the inferior thyroid artery, and some of it comes from the anastomotic branch between the superior thyroid artery and the inferior thyroid artery. The blood supply of inferior parathyroid gland mainly comes from inferior thyroid artery<sup>[6, 11]</sup>. The Parathyroid hormone (PTH) is mainly produced by the Parathyroid glands. PTH is a linear peptide with 84 amino acids secreted by the host cells of parathyroid gland, and its biological activity is determined by the 1-27 amino acid residues at the n-terminal. Its half-life was about 5min in plasma, and it was mainly inactivated in kidney<sup>[12]</sup>. Its main function is to regulate the metabolism of calcium and phosphorus in the body. The main target organs of PTH action are bone and kidney, which mobilize bone calcium into the blood and promote the reabsorption of calcium ions and the excretion of phosphate in renal tubules, so as to increase the level of blood calcium and decrease the level of blood phosphorus. In addition, PTH also indirectly promotes the intestinal absorption of calcium ions<sup>[13, 14]</sup>. When tumor surgery, illness, or other causes

PTH secretion decline, will cause the body hypocalcemia, and low blood calcium level will cause different clinical symptoms, light person such as oral and extremities numbness, cramps nervous system performance, the person that weigh can have syncope, arrhythmia, such as system performance, there are even suffocation crisis due to laryngospasm patient safety<sup>[15]</sup>. The role of PTH is so important, and in the thyroid surgery, parathyroid anatomical morphology and adipose tissue, lymphoid tissue is very close to the naked eye to distinguish the difficulty of a relatively large, and many patients parathyroid smaller or some position variation is larger, more increased injured or accidentally cut the risk of parathyroid gland, so parathyroid recognition and protection is of great urgency.

According to relevant studies, the incidence of postoperative HPT can be as high as 52%<sup>[16, 17]</sup>. If the duration of parathyroid hypofunction is longer than 6 months, it is considered as permanent HPT, while if the duration is less than 6 months, it is considered as temporary HPT. Cavicchi O, Wong KP et al<sup>[18, 19]</sup> found that postoperative temporary HOP was more common, with an incidence of 3%~55%, while permanent HPT was only 0.4%. The incidence of hypocalcemia is also high in patients undergoing thyroid surgery. Patients undergoing total thyroidectomy are more prone to hypocalcemia, up to 55%<sup>[20]</sup>. Some scholars have confirmed that hypocalcemia will occur even if the blood PTH level is within the normal range after surgery, which indicates that it is very important and necessary to ensure the integrity of the parathyroid gland<sup>[21]</sup>.

In order to reduce the incidence of postoperative hypoparathyroidism, surgeons in recent years have been trying to find ways to improve and ensure better results, and strive to protect the parathyroid gland during operation. At present, the most widely used intraoperative parathyroid gland recognition method is the in situ parathyroid gland protection technology based on anatomy. Paek et al. <sup>[22]</sup> reported that in the first two years of practice, surgeons treated 6.5 percent of patients with permanent parathyroid dysfunction, which dropped to 1.8 percent in the following two years. Lack of surgical experience is an important risk factor for permanent hypoparathyroidism, so surgeons are constantly looking for accurate, reliable and simple ways to distinguish parathyroid and non-parathyroid

tissue. As many techniques applied to the identification of a parathyroid: Methylene blue, Nano carbon and 5 - amino levulinic acid (5 ALA) such as dye which can realize the parathyroid gland is dyed or negative staining, radionuclide, endoscopy, near-infrared fluorescence<sup>[23]</sup> and sound radiation pulse elasticity imaging, dynamic optical contrast imaging technology development, also to try to identify parathyroid gland; Rapid frozen pathological examination is the gold standard to distinguish parathyroid gland from non-parathyroid gland, but both of them have some shortcomings.

The satisfactory removal of all hyperfunctioning parathyroid tissues using intraoperative serum PTH assays was first reported in 1988, and serum PTH is now considered the gold standard for diagnosing hyperfunctioning parathyroid tissues. With the development of FNA technology, one method is to identify the suspected parathyroid hormone (rIO-PTH) tissues in surgery by rapid Intraoperative parathyroid hormone (FNA) assay. As early as 2000, Perrier et al.<sup>[24]</sup> reported the feasibility of this method, and the sensitivity and specificity of this study were 100%. Kiblut et al.<sup>[25]</sup> reported a prospective trial in 170 patients and came to the same conclusion. Lamont et al.<sup>[26]</sup>, Pelizzo et al.<sup>[27]</sup>, Guerrero et al.<sup>[28]</sup> also reported the feasibility of clinical application of this method. In this study, we used this method to intraoperative identify and protect parathyroid tissues, and carried out a comparative study to explore the feasibility, advantages and disadvantages of this method. In this study, PTH values measured by FNA from 145.2 to 5000pg/L were identified as parathyroid tissues according to the studies of Bian Xuehai and Maria et al., and those lower than the value were identified as non-parathyroid tissues. In our study, A group for the blank control group, group B using the method of FNA intraoperative rapid determination of parathyroid hormone, and from the number of intraoperative identification of parathyroid, PTH and postoperative patients blood calcium levels, hypocalcemia and parathyroid function decline in the incidence of this A few aspects to study, the results suggest that the identification method of group both on the identification number of parathyroid and postoperative blood calcium and PTH levels, the incidence of postoperative complications in significantly better than the blank group. A total of 91 parathyroid glands were identified in group A, with an average of (2.6±0.3). A total of 105 parathyroid glands were identified in group B, with an average of (3.0±0.2). P < 0.05 was compared between the two groups. Postoperative serum calcium and PTH levels in group B were significantly higher than those in group A, and the differences were statistically significant. As for the incidence of postoperative complications, group A without any protective measures was significantly higher than

group B. No serious complications occurred in either group in the study, on the other hand, that the rIO-PTH method did not increase the risk of additional surgery and was safe.

According to the above results show that, as a kind of new method of recognition and protection of the parathyroid gland, rIO-PTH method in intraoperative has good recognition effect of parathyroid, which can effectively distinguish between parathyroid tissue and non parathyroid tissue, and for the function of the parathyroid gland has good protection effect, and can reduce the postoperative hypocalcemia and the incidence of parathyroid function impairment. The safety and practicality of this technique are effective for the protection of parathyroid glands that are difficult to be recognized during surgery and for the improvement of parathyroid gland recognition by inexperienced surgeons.

As a new technology, rIO-PTH was not fully proficient in the initial puncture operation, which may have interfered with the determination of PTH due to puncture, but this situation was avoided after the practice of pre-experiment. We believe that with the increase of the number of cases, skilled operation can improve the situation. In the study, according to the effect of the recognition and protection, rIO-PTH is a relatively cheap technology, its less expensive for Nano carbon, and the technology can effectively identify and protect the parathyroid gland, rapid, simple, and even can replace the frozen section and Nano carbon, in the majority of the recognition and protection of parathyroid technology especially in a place, and have very big development space.

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