



## Intraoperative Needle Aspiration Parathyroid Hormone Levels for Diagnosis of Abnormal Parathyroid Glands and Intraoperative Localization of Parathyroid Glands

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### Abstract

**Introduction:** The success of parathyroidectomy depends on two important factors: accurate surgical recognition of abnormal parathyroid glands and pathological parathyroid confirmation of removed tissues. Needle aspiration for parathyroid hormone level has been applied to distinguish parathyroid from non-parathyroid tissues, with high accuracy. However, up until now there has been no cut-off value for the diagnosis of hyperfunction parathyroid glands.

**Objective:** To define the cut-off value of intraoperative needle aspiration parathyroid hormone level for the diagnosis of hyperfunctioning parathyroid glands and intraoperative localization of parathyroid glands.

**Methods:** A cross-sectional study was conducted in 35 hyperfunctioning parathyroid glands, and 35 normal parathyroid glands. Needle aspiration was performed during thyroid/parathyroid surgery. The aspirated tissues were washed with 5 mL of normal saline solution and immediately sent for parathyroid hormone analysis.

**Results:** The median parathyroid hormone levels were 2823 pg/mL, (IQR: 1871.1–5000) and 61.37 pg/mL, (IQR: 29.69–272.7) for the hyperfunctioning parathyroid and the normal parathyroid glands, respectively. The cut-off level of hyperfunctioning parathyroid gland was detected at 1050 pg/mL, with sensitivity and specificity more than 90%.

**Conclusion:** The cut-off value of intraoperative needle aspiration parathyroid hormone levels can differentiate not only parathyroid from non-parathyroid tissues but also hyperfunctioning parathyroid from normal glands. Whilst, when applied with other diagnostic tools, the high level of intraoperative needle aspirated parathyroid hormone can potentially yield useful information towards successful management of hyperparathyroidism. In our post-operative follow up period of 4 months to 2 years, there have been no recurrent or persistent hyperparathyroidism.

**Keywords:** Parathyroid hormone; Parathyroid gland; Parathyroidectomy

### Introduction

The success of parathyroidectomy depends on two important factors: accurate surgical recognition of abnormal parathyroid glands and pathological parathyroid confirmation of removed tissues. Frozen section is usually employed primarily to confirm the presence of parathyroid tissues, especially in the re-operation cases. In those cases, normal anatomic relations are disturbed by scarring and adhesion. Needle aspiration for parathyroid hormone level could effectively distinguish parathyroid from non-parathyroid tissues. The level of more than 84 pg/ml yields 100% sensitivity and specificity, which is suggestive for the presence of PTH-secreting tissues. Following the advice from biologists, the fine needle intra glandular aspiration technique has been developed and referenced by several research articles [1-6]. Nevertheless, the range of PTH level of hyperfunctioning glands is 8,169 +/- 2,597 pg/mL [7]. Up until now, there has been no applied cut-off value of needle aspiration PTH level for the differentiation of hyperfunctioning parathyroid from normal glands. Hence, we aimed to define the cut-off value of needle aspiration PTH level for accurate diagnosis of hyperfunctioning parathyroid glands and localization of parathyroid glands.

With a significant clinical implication, the optimal cut-off value from our study could be applied in intraoperative quick assay as a simple procedure to distinguish between normal and hyperfunctioning parathyroid glands [8].

### OPEN ACCESS

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## Materials and Methods

### Study design

This cross-sectional study was conducted at Department of Otolaryngology, in cooperation with Department of Clinical Pathology, Siriraj Hospital, Mahidol University, between February 2016 and December 2017. The study was approved by Siriraj Institution Review Board (SIRB), and granted by Faculty of Medicine, Siriraj Hospital, Mahidol University.

### Participants

Patients, aged over 18 years, were included. One group was diagnosed with hyperparathyroidism and indicated for parathyroidectomy. The other group was indicated for thyroid surgery and agreed to participate in the normal parathyroid group in this clinical research. Exclusion criteria were patients in the normal parathyroid group who took drugs or supplements with an effect to the level of parathyroid hormone such as calcium >1500 mg/day, phosphates, anticonvulsants, steroids, isoniazid, lithium and rifampicin, or those with hypercalcemic symptoms such as polyuria, polydipsia, nocturia, and diagnosed with nephrolithiasis, nephrocalcinosis and pancreatitis. Also, those in the hyperfunctioning parathyroid group without the pathological report of hyperfunctioning parathyroid glands such as parathyroid adenoma, parathyroid hyperplasia, and parathyroid carcinoma were excluded [9-14].

### Methods

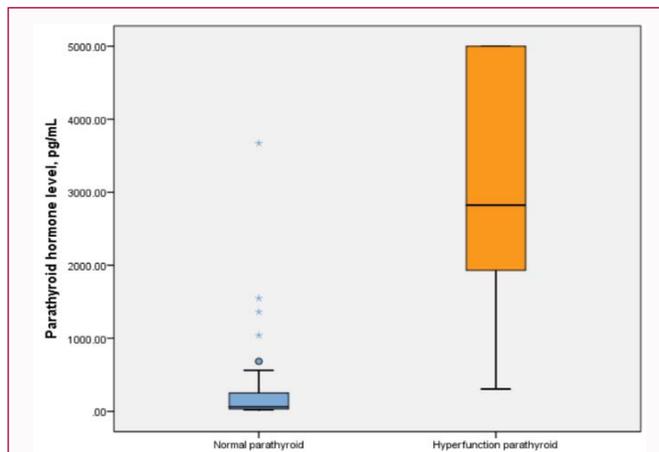
The study was performed in 35 hyperfunctioning parathyroid glands (abnormal parathyroid group) and 35 normal parathyroid glands (normal parathyroid group). In the abnormal parathyroid group, under direct vision, 25-gauge needle was used to aspirate an *ex vivo* parathyroid tissue. Strictly only five passes were allowed to obtain a sufficient sample. Samples were collected by adding 5 ml of saline solution, and then injected into Ethylene Diamine Tetra Acetic Acid (EDTA) tubes for analysis. The confirmed characteristics of parathyroid included: 1) Location (superior parathyroid gland; cricothyroid junction, posterior capsule of superior pole, pre-tracheal fascia, inferior parathyroid gland; Inferior pole of thyroid, area 2 cm, 1 cm above crossing of inferior thyroid artery and recurrent laryngeal nerve, 2) Color (yellow-reddish brown flat ovoid), and 3) Size (5 mm to 8 mm long, 3 mm to 5 mm wide, and 1 mm 2 mm antero-posteriorly). To obtain a normal parathyroid tissue, an *in vivo* aspiration was performed with the same method as mentioned. The vials of both groups must be transferred for PTH analysis using Electrochemiluminescence Immunoassay by Roche Cobas 8000 system within 30 minutes.

### Statistical analysis

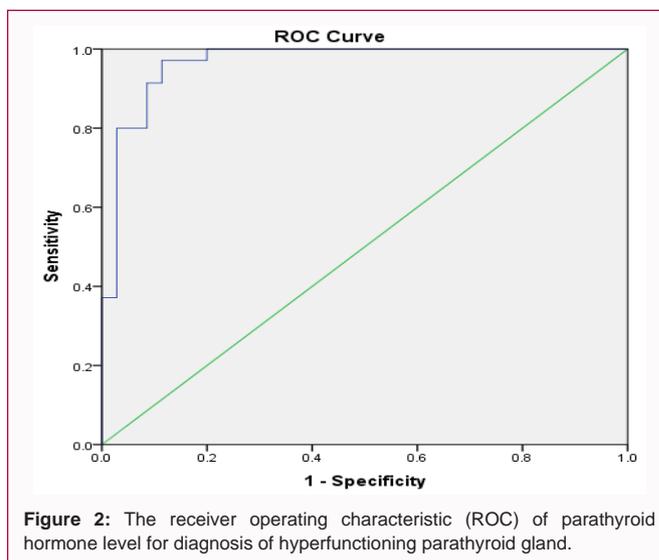
Both groups of patients were non-normal distributed, thus Mann-Whitney test was used to compare between the two groups. Parathyroid hormone level was stated in pg/mL. Values were defined as median and interquartile range (IQR). Performance of cut-off values was determined from Receiver Operating Characteristic (ROC) curve analysis, using pathological report as reference method and PTH measurements in needle aspiration samples as testing method. Sensitivity and specificity were calculated. Statistical analysis was performed by using SPSS window version 18.0 (SPSS Inc., Chicago Illinois). P-value of less than 0.05 was considered statistically significant.

## Results

A total of 70 aspirated tissue samples (35 hyperfunctioning



**Figure 1:** Parathyroid hormone concentration in needle aspiration classified as hyperparathyroid and normal parathyroid. The box lines represent (from the top) the third quartile, the median, and the first quartile.



**Figure 2:** The receiver operating characteristic (ROC) of parathyroid hormone level for diagnosis of hyperfunctioning parathyroid gland.

parathyroid glands and 35 normal parathyroid glands) were taken from 40 patients of 30 males and 10 females, with mean age of  $51.72 \pm 12.3$  in the normal parathyroid group and  $56.8 \pm 13.7$  in the hyperfunctioning parathyroid group. After parathyroidectomy, the pathological report revealed 30 parathyroid hyperplasia and 5 parathyroid adenomas in the hyperfunctioning parathyroid group (Figure 1). The aspiration of 35 hyperfunctioning parathyroid glands was correlated with their pathological diagnosis. There was difference between PTH levels of hyperfunctioning parathyroid glands (2823 pg/mL, IQR: 1871.1–5000) and normal parathyroid glands (61.37 pg/mL, IQR: 29.69–272.7), with statistical significance ( $p < 0.005$ ; Mann-Whitney test).

The ROC curve analysis of PTH in tissue aspiration wash yielded an area under the curve (AUC) of 0.96 (Figure 2). To achieve the sensitivity and specificity higher than 90% for differentiating between hyperfunctioning and normal glands, the cut-off level at 1050 pg/mL was considered. The positive predictive and negative predictive values were both at 91.4% (true positive:  $n=32$ ; true negative:  $n=32$ ; false positive:  $n=3$ ; false negative:  $n=3$ ). The reference range of abnormal gland from tissue aspirated was 957.48–5000 pg/mL, defined by  $p_{10}$ – $p_{90}$ . The association between parathyroid hormone levels from

aspirated tissues and other clinical parameters were calculated using Spearman's rho correlation coefficient (rs). These parameters included pre-surgical serum parathyroid hormone [rs=0.27(p=0.117)] and weight of hyperfunctioning parathyroid gland [rs=0.146(p=0.442)]. These results suggested no correlation between parathyroid hormone from aspirated tissue and pre-operative serum parathyroid hormone level and weight of hyperfunctioning parathyroid gland. In addition, following the pathological results, there was no significant difference between parathyroid hormone level taken from parathyroid adenoma (1871.1 pg/mL, IQR 1010.1-3528.0) and parathyroid hyperplasia (3028 pg/mL, IQR 2152-5000) (p=0.141). Nonetheless, Spearman's correlation coefficient showed that parathyroid hormone level from tissue aspirate was associated with the size of hyperfunctioning gland [rs=0.569 (p< 0.001)], and pre-operative corrected serum calcium [rs=0.73 (p<0.01)] [15].

## Discussion

Over decades, there have been built-up technological advancements in parathyroid surgery, which allows the directed removal of hyperfunctioning parathyroid glands in many instances, without requiring exploration of all 4 glands. However, 6% of the cases still have persistent or recurrent diseases [16]. Intraoperative PTH assay is then proposed as a quick and a simple method with high sensitivity and specificity to decline the incidence of reoperation [6].

Following the literature review, there are only a few studies advocating intraoperative tissue aspiration for parathyroid hormone level as a confirmation method during parathyroidectomy [1,4-6,17-20]. In consistency was found in intraoperative aspiration in term of tissue aspiration techniques and amount of dilution. In the meantime, some researchers applied these techniques *in vivo*, while others preferred to apply them in *ex vivo* parathyroid tissues. Nevertheless, most authors agreed that direct aspirated tissue wash could be used as a biochemical frozen section to confirm the presence of parathyroid tissues.

In this study, the intraoperative aspiration for PTH method was highly accurate to distinguish hyperfunctioning from normal parathyroid glands. The value higher than 1050 pg/mL could confirm tissue diagnosis of hyperfunctioning parathyroid with specificity of 91.4%.

There have been widely reports on PTH value from parathyroid tissue aspiration. In normal parathyroid tissues, the result from our study was consistent with other published studies. This value was significantly different from the level of hyperfunctioning glands. Unexpectedly, some detected PTH levels from hyperfunctioning parathyroid were reported to be lower than normal parathyroid. This might be the result of non-standardized aspiration techniques and different characteristics of parathyroid glands.

Parathyroid hormone level from the aspiration washed of the suspected parathyroid gland can be a quick, low cost and simple technique, but it is an operator-dependent method. The more passes of the needle into the gland indicate higher PTH levels, thus strictly 5 passes should be suggested for sufficient tissue aspiration.

Re-operative parathyroidectomy has more failure rate and morbidity. Without intraoperative PTH level, the identification of parathyroid glands is based only on macroscopic findings, such as color, consistency, size, and location in the neck. Fibrosis from previous procedures may make parathyroid identification even

more difficult and increase the risk of recurrent laryngeal nerve injury. Thus, accurate localization is considered as the foundation of successful management of reoperation in patients.

## Conclusion

The cut-off value of intraoperative needle aspiration parathyroid hormone levels can both differentiate parathyroid from non-parathyroid tissues and distinguish hyperfunctioning parathyroid from normal glands. The needle aspirated parathyroid hormone level higher than 1050 pg/mL could confirm tissue diagnosis of hyperfunctioning parathyroid with specificity of 91.4%. When applied with other diagnostic tools, the high level of intraoperative needle aspirated parathyroid can potentially yield useful information towards high diagnosis accuracy and successful management of hyperparathyroidism.

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