

# Intraoperative Intact Parathyroid Hormone Level Monitoring as a Guide to Parathyroid Reimplantation after Thyroidectomy

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**Objective:** The goal of this study was to determine whether intraoperative intact parathyroid hormone (IOiPTH) levels can predict the functional status of remaining parathyroids at the end of total thyroidectomy and thereby be a guide for parathyroid autotransplantation when glands are deemed not functional. **Study Design:** Prospective study involving 23 patients undergoing either total thyroidectomy or completion thyroidectomy. **Methods:** During surgery, an attempt was made to identify all four parathyroid glands. Normal size vascular glands were preserved, whereas avascular glands were microdissected and reimplanted. Serial IOiPTH was measured preoperatively after each parathyroid was identified, manipulated, or removed and serum iPTH measurements were done postoperatively up to 56 days. **Results:** The sensitivity of low IOiPTH in identifying a devascularized gland was 88.9%, and specificity was 92.9%. A normal IOiPTH level indicates at least two functioning glands. IOiPTH levels between 1.5 and 10 pg/mL indicate only one functional gland. Undetectable IOiPTH levels indicate no residual functioning gland. **Conclusions:** For patients undergoing total or completion thyroidectomy, IOiPTH should be routinely measured at the end of the procedure, and a level less than 10 pg/mL requires reassessment of remaining parathyroid glands. Vascularized glands should be preserved regardless of IOiPTH levels. Devascularized glands or glands of questionable vascularity should be considered for autotransplantation. **Key Words:** Parathyroid hormone, parathyroidectomy, thyroidectomy.

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## INTRODUCTION

Patients undergoing total thyroidectomy may be rendered permanently hypoparathyroid and hypocalcemia by either inadvertent removal of parathyroid glands or more commonly by devascularization of preserved parathyroid glands. An intraoperative test to assess function of parathyroid glands could be a useful tool to detect inadequate parathyroid gland function secondary to devascularization and determine which glands should be removed from their beds and autotransplanted into the sternocleidomastoid muscle. Proactive identification and treatment of injured parathyroid glands may reduce the incidence of permanent hypocalcemia as a complication of total thyroidectomy.

The goal of this study was to determine whether intraoperative intact parathyroid hormone (IOiPTH) levels can predict the functional status of remaining parathyroids at the end of total thyroidectomy and thereby be a guide for parathyroid autotransplantation when the glands are deemed not functional.

## MATERIALS AND METHODS

Institutional review board approval was received for a prospective study of consecutive patients undergoing either total or completion thyroidectomy at a tertiary level referral hospital. The study was explained to prospective patient groups, and each patient signed a written informed consent form during an office visit before their scheduled procedure. A preoperative blood sample was drawn for baseline measurement of serum IOiPTH and serum calcium concentrations. Thyroidectomy patients whose disease warranted less than a total thyroidectomy were dropped from the study when this fact became apparent.

IOiPTH and intact parathyroid hormone (iPTH) were measured using an automated two-site sandwich immunoassay chemiluminescence system (ACS 180, Bayer Health care, Pittsburgh, PA). The ACS 180 Intact PTH assay measures intact PTH concentrations up to 1,900 pg/mL and a minimum detectable concentration of 1.5 pg/mL. The normal range for apparently healthy individuals is between 11.1 and 74 pg/mL.

A total of 23 patients underwent total thyroidectomy with or without mediastinal lymphadenectomy during the study period. During total thyroidectomy, we always attempted to identify and

preserve of all four parathyroids. As each gland was identified, an assessment was made regarding its vascularity. Standard criteria for evaluating vascularity included the following protocol. If the gland appeared normal on visual inspection with an intact vascular pedicle, it was initially deemed "vascularized." If there was a question of color change or no apparent vascular pedicle preserved, the gland was incised for 1 mm to assess bleeding. Absence of bleeding changed the status of the gland to "avascular." Parathyroid glands found within the capsule of the thyroid were dissected out and removed for reimplantation after histologic confirmation; these were obviously identified as "avascular." Bleeding with bright red blood after the diagnostic incision indicates a vascular gland, whereas the absence of any bleeding or minimal bleeding of dark venous blood indicates an avascular gland. Fifteen minutes after dissection of each parathyroid gland, blood was drawn for serum IOiPTH and calcium levels. If IOiPTH dropped to below normal values (11–74 pg/mL), all "vascularized" glands previously left intact were reassessed and tested for vascularity with small incisions. Parathyroid glands identified as "avascular" were removed and confirmed by frozen section, microdissected, and re-implanted in the sternocleidomastoid muscle. After surgery, serum iPTH and calcium levels were measured in the recovery room and on postoperative days 1, 7, 14, 21, 28, and 56. The laboratory normal serum iPTH value was 10 to 65 pg/mL. In 18 of 23 patients, four parathyroid glands were identified. In the remaining five patients, three glands were identified.

## RESULTS

Twenty-three patients underwent total thyroidectomy, of which 21 had a total thyroidectomy as their initial procedure. Two patients were referred after partial thyroidectomy with evidence of residual disease and were in need of a completion thyroidectomy. One of these patients also had two parathyroids removed with the initial surgery. Sixteen patients had papillary carcinoma of the thyroid, one had follicular cell carcinoma, three had benign bilateral follicular neoplasm, and three had multinodular goiter.

### *Intraoperative iPTH Levels during Thyroid Surgery*

In 14 patients, IOiPTH levels remained in the normal range throughout the procedure. However, in two of these patients, iPTH levels dropped below the normal by postoperative day 7. In the other nine patients, IOiPTH levels dropped below normal during the procedure. In four patients, avascular glands were diagnosed on visual inspection, and these parathyroid glands were reimplanted. In four other patients, parathyroid glands appearing "vascular" on visual inspection were discovered to be "avascular" glands when incised. These glands were excised and reimplanted. Glands that appeared vascular on initial dissection after completion of surgery on one side were sometimes reassessed after the second side dissection was completed if IOiPTH levels identified a problem. In one patient, vascular assessment by incision demonstrated a "vascular" gland despite a low IOiPTH level. These glands were not reimplanted.

### *Clinical Observations*

The following observations were noted with respect to the relationship between the number of functioning

glands and the IOiPTH level as well as the postoperative iPTH levels:

1. All the patients with four intact glands ( $n = 21$ ) had normal or elevated iPTH levels (1 patient with no clinical history of hyperparathyroidism and no evidence of parathyroid abnormalities had a preoperative iPTH level of 218 pg/mL [normal 10–65 pg/mL]).
2. After devascularization or removal of one parathyroid, iPTH levels remained normal in all patients ( $n = 17$ ) (Fig. 1).
3. After devascularization or removal of two parathyroids, iPTH levels still maintained the normal levels in all patients ( $n = 13$ ). There was no significant difference between IOiPTH levels representing two, three, or four functioning glands (Fig. 1).
4. After devascularization of three parathyroids, all patients dropped to subnormal levels (between 2.5 and 11 pg/mL,  $n = 8$ ) (Fig. 1).
5. After devascularization or removal of four parathyroids, iPTH became nondetectable ( $n = 2$ ) (Fig. 1).
6. Patients with normal iPTH level at the end of surgery can develop subnormal levels after surgery ( $n = 2$ ).

### *Sensitivity and Specificity*

Because normal IOiPTH levels are maintained when two, three, or four parathyroid glands are intact, IOiPTH level cannot differentiate parathyroid injury unless three or more glands have been removed or devascularized. The sensitivity of IOiPTH in detecting inadequate parathyroid gland function was determined using the formula

$$\text{Sensitivity (\%)} = \left( \frac{\text{TP}}{\text{TP} + \text{FP}} \right) \times 100 \quad (1)$$

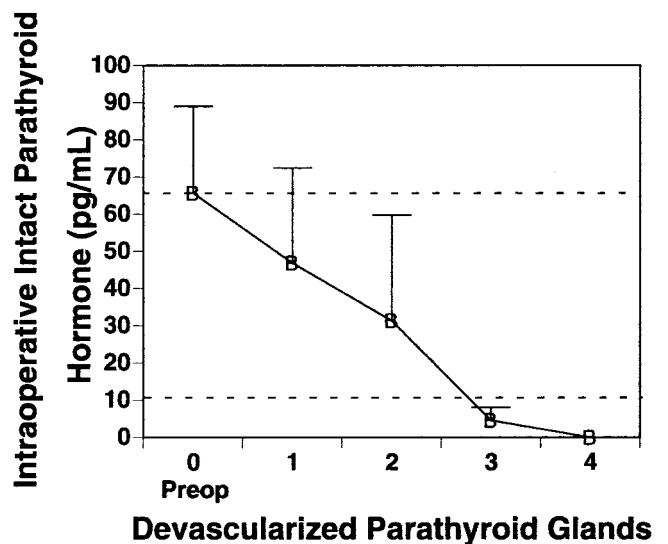


Fig. 1. The mean intraoperative intact parathyroid hormone (IOiPTH) levels after sequential removal/devascularization of parathyroid gland during thyroidectomy. Note there is no significant difference between IOiPTH levels representing zero, one, or two devascularized/removed parathyroid glands.

where TP = true positive ( $\geq 3$  parathyroid glands removed or devascularized and IOiPTH  $< 10$  pg/mL), and FP = false positive ( $< 3$  parathyroid glands removed or devascularized and IOiPTH  $< 10$  pg/mL).

Fourteen patients maintained a normal IOiPTH level even after dissection of all four parathyroids. The remaining nine patients had their IOiPTH levels drop below normal ( $< 10$  pg/mL). On the basis of clinical evidence, eight of the nine patients had three or four devascularized parathyroid glands. This translated into a sensitivity of 88.9%.

The specificity IOiPTH in detecting inadequate parathyroid gland function was determined using the formula

$$\text{Specificity (\%)} = \left( \frac{\text{TP}}{\text{TP} + \text{FP}} \right) \times 100 \quad (2)$$

In one patient, IOiPTH remained within normal limits despite the fact that clinical evidence showed that three or four parathyroid glands were devascularized. Thus, the specificity of monitoring IOiPTH in this group was 92.9%.

### Complications

There were no intraoperative or postoperative complications. Twenty-two patients were discharged home on postoperative day 1 and required no intravenous calcium. Twelve of these patients were discharged home with oral calcium and vitamin D supplements that were tapered over the next 7 to 56 days. One patient who had previous removal of two parathyroids and intraoperative reimplantation of a third avascular parathyroid gland that required 24 hours of intravenous calcium supplements was discharged on postoperative day 2.

### DISCUSSION

Thyroid surgery in the hands of experienced surgeons is currently one of the safest procedures performed. Nevertheless, as with every surgical intervention, it bears certain complications. Some of these (e.g., hematoma, seroma) can be easily managed, whereas others (e.g., recurrent laryngeal nerve injury and hypocalcemia) are quite significant. Although the introduction of intraoperative monitoring of the recurrent and superior laryngeal nerves may decrease the risk of nerve injury, the risk of permanent hypoparathyroidism and hypocalcemia has not decreased. Prediction of postoperative hypocalcemia is difficult because of multifactorial causes, which involve previous thyroid status (thyrotoxicosis), extent of surgery (completion surgery, neck dissection, retrosternal extension) and removal of more than one parathyroid gland, macrodilution, hypomagnesemia, medications, and general anesthesia.<sup>1</sup>

Although transient hypocalcemia is quite common after thyroidectomy, permanent hypoparathyroidism and hypocalcemia are rare yet occur in a certain percentage of patients. This study focuses on a technique that may identify those patients at risk for permanent hypoparathyroidism at a point where the surgical plan can be altered to attempt reduction of the incidence of permanent hypoparathyroidism. Clearly, the risk of permanent hypoparathy-

roidism varies at different centers, but several larger series report a significant incidence. In a study of 790 patients, Bergamaschi et al.<sup>2</sup> reported the following incidences of hypocalcemia: 17.4% in 86 patients undergoing thyroidectomy and neck dissection; 10.2% in 59 patients undergoing completion thyroidectomy; and 2.8% in 645 patients undergoing total thyroidectomy. In addition, Battacharyya and Fried et al.<sup>3</sup> reported a 6.2% incidence in 517 patients. Other studies reported lower incidences; however, those investigators did not routinely measure calcium levels, but rather, they monitored only the symptomatic patients.<sup>4</sup> Extensive procedures increase the risk of parathyroid devascularization and removal. Each surgeon can assess his or her own experience in determining those patients at risk of permanent hypoparathyroidism depending on the nature and extent of the surgery.

Many studies have evaluated low IOiPTH level as a predictor of postoperative hypocalcemia.<sup>5-8</sup> These studies, although very convincing, fall short of serving any real practical purpose. This study is based on the premise that a devascularized parathyroid gland is not always recognizable by visual inspection of the gland. Therefore, although glands are often microdissected and reimplanted when they are intracapsular or clearly devascularized, a significant percentage of patients with "normal" appearing glands during surgery suffer from postoperative hypoparathyroidism and hypocalcemia. In four of our nine cases, we found "normal" parathyroid glands, which were avascular on incisional biopsy assessment. Similar results were reported by Kuhel and Carew.<sup>9</sup> They reported that visual inspection is a poor tool to assess vascularity of parathyroid glands.<sup>9</sup> On the other hand, routine incision of all glands may increase manipulation and injury of intact glands. Obviously, an objective test of gland function without manipulation of the gland would be ideal.

A valuable test would to identify potential hypoparathyroidism intraoperatively and allow the surgeon to alter the surgical plan to forestall postoperative hypocalcemia. A low IOiPTH level may be an indicator of vascular injury of an intact gland and may be a guide to more aggressive assessment of the vascularity in the gland, and if not adequate, would lead to microdissection and autotransplantation of the gland.

Autotransplantation of devascularized parathyroid gland in the majority of cases prevents permanent hypoparathyroidism, with a failure rate in the range of 1% to 6%.<sup>10-12</sup> A major disadvantage of this approach is development of transient hypocalcemia because reimplanted glands achieve normal function only after 3 to 14 weeks.<sup>13-14</sup> Therefore, all normal, viable parathyroid glands should be preserved in situ. In our series of thyroidectomy patients, we found full recovery of parathyroid function at day 28 to 56, with a mean parathyroid hormone level of 30 to 45 pg/mL (Fig. 2). Our study shows 88.9% sensitivity and 92.9% specificity of low ( $< 10$  pg/mL) IOiPTH level in identifying patients with avascular parathyroid glands. In eight of nine cases that underwent autotransplantation, IOiPTH level ranged between 1.5 and 4.2 pg/mL, indicating only one functioning parathyroid gland.

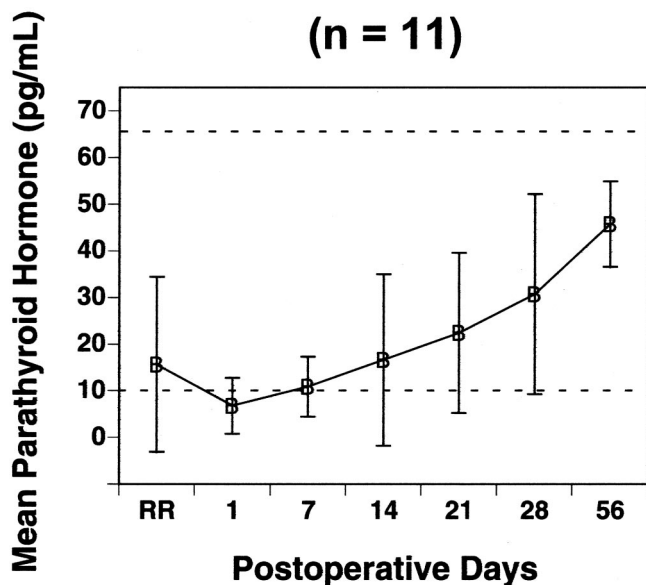


Fig. 2. Recovery of the implanted parathyroid glands as measured by serum intact parathyroid hormone (iPTH) levels in patients with more than three parathyroid gland injuries or devascularizations.

At least two viable parathyroid glands are required to maintain postoperative parathyroid hormone levels within the normal range. In our study, 10 patients were identified with subnormal IOiPTH levels, and 9 of these had devascularized glands. On the other hand, removal or devascularization of the one or two glands kept IOiPTH levels within the normal range (Fig. 1). Removal of all four glands should make IOiPTH undetectable, which is a logical sequel (with the possible exception of supernumerary parathyroid glands). It is evident that IOiPTH reflects functional parathyroid gland status during surgery. Therefore, IOiPTH levels within a normal range indicates parathyroid gland potency to maintain normal parathyroid hormone level. On the other hand, a drop in parathyroid hormone levels below a normal range (<10 pg/mL) should be accepted as a permanent injury of three parathyroid glands until proven otherwise, which will result in development of postoperative hypoparathyroidism. In the case of low IOiPTH (<10 pg/mL), reexploration and assessment of vascularity of the preserved parathyroid glands is required (Fig. 3). In situ preservation of vascularized glands and autotransplantation of avascular glands would be sufficient to prevent postoperative hypoparathyroidism in most patients.

As with most tests, this one has a certain margin of error and is meant to be a guide to the surgeon rather than an absolute indication for transplantation. In our study, there were both some false-positives and a false-negative. In two cases, intraoperative IOiPTH levels were normal, but the postoperative iPTH level dropped to 5 and 3 pg/mL at postoperative day 1 and 7 but then returned to a normal range at postoperative day 14 and 21. Such postoperative decrease of parathyroid hormone level might be explained as transient latent injury to parathyroid glands caused by vascular spasm, leading to ischemia of the gland and possible necrosis. Fortunately, intact vascular supply and

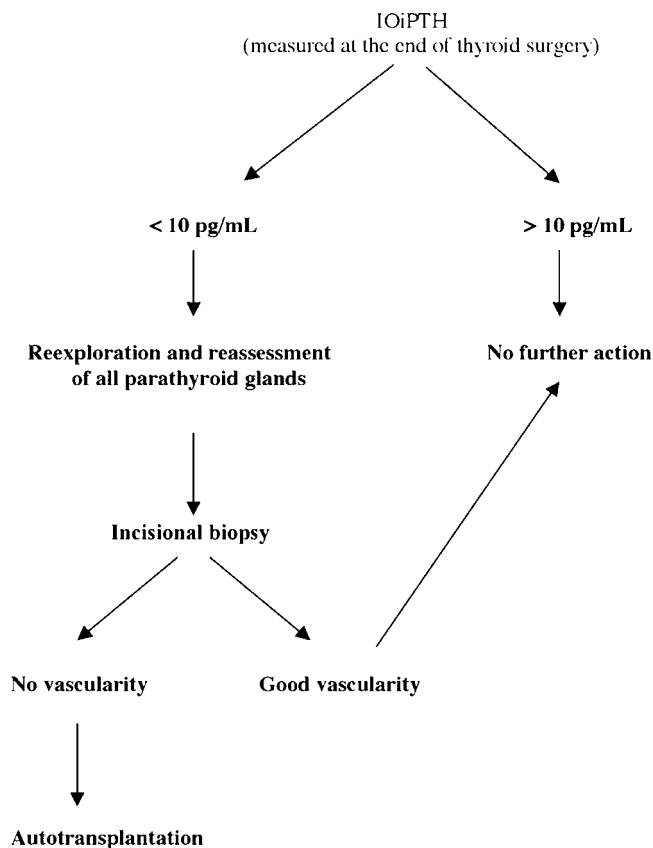


Fig. 3. Algorithm for the use of intraoperative intact parathyroid hormone (IOiPTH) level monitoring at the end of thyroidectomy to assess parathyroid function.

parathyroid gland ability to regenerate made the hypoparathyroid state transient in these patients.<sup>15</sup> One patient had a false-negative test. Her IOiPTH level dropped below normal, but clinical assessment of her glands indicated adequate vascularity. Those glands, therefore, were not reimplanted.

This study cannot prove that a low IOiPTH level indicates permanent parathyroid injury. It only reflects the parathyroid gland function at the time of assay. In fact, in one of our patients with low IOiPTH, we felt that clinical evaluation indicated normal vascularity, and we elected to preserve the parathyroid glands in situ. We are not advocating routine autotransplantation of all parathyroid glands. We are suggesting that assessment of parathyroid vascularity by clinical inspection only is less than 100% reliable, even to an experienced surgeon (M.F., senior author), who has routinely assessed parathyroid vascularity in over 1,000 patients. The value of IOiPTH measurement is to alert the surgeon for the need for more definitive assessment or a reassessment of previously examined glands. This may require incising the gland to assess vascularity.

Although parathyroid autotransplantation is dependant on the philosophy of the surgeon, many surgeons do autotransplant nonvascular glands and could benefit from a test that would help identify those glands in need of autotransplantation. In a large series of patients (271), Lo



and Lam<sup>16</sup> compared patients who underwent total thyroidectomy with or without autotransplantation. They noted that none of the 96 patients in whom parathyroid glands were autotransplanted became permanently hypoparathyroid.<sup>16</sup> In a later study, Lo and Tam<sup>13</sup> showed that the biochemical function of parathyroid autograft during thyroid surgery can be determined objectively. They concluded that routine parathyroid autotransplantation is not recommended, but devascularized parathyroid should be routinely transplanted. Low IOiPTH level should alert the surgeon that preserved in situ glands may not be functional. We are, therefore, only suggesting that a low IOiPTH level should alert the surgeon that preserved in situ glands might not be functional. The surgeon may then use his or her clinical judgment as to whether autotransplantation is indicated.

The cost of a single "stat" IOiPTH measurement at the end of a total thyroidectomy is approximately \$309 at our institution, with the results available in 10 to 15 minutes. We believe that this cost can easily justify this type of monitoring because it leads to a reduced incidence of permanent hypoparathyroidism and its associated costs. In addition to the long-term benefits, early identification of a low IOiPTH will lead to earlier treatment for hypocalcemia. This early intervention allows for discharge of patients usually within 24 hours after surgery.<sup>17</sup>

## CONCLUSIONS

In patients undergoing total thyroidectomy, devascularization of one or two parathyroid glands cannot be detected by measurement of IOiPTH level. There is no statistical difference between levels that represent two, three, or four functioning glands (all >10 pg/mL). Devascularization of three glands will result in an IOiPTH level below normal (<1.5–10 pg/mL). Devascularization of all four glands will result in an undetectable IOiPTH level. For patients undergoing total or completion thyroidectomy, IOiPTH level less than 10 pg/mL should alert the surgeon to the need for parathyroid gland reassessment. Because the low IOiPTH level may reflect transient ischemia, we are not recommending routine autotransplantation in every patient, but rather we are recommending this as an indication for aggressive reassessment of each gland vascularity and for autotransplantation when devascularization is evident.

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