

# The value of intraoperative PTH measurements in patients with mild primary hyperparathyroidism

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## Abstract

**Purpose** Intraoperative parathyroid hormone (ioPTH) measurement has facilitated a move to minimally invasive parathyroidectomy. Patients are referred for surgery earlier with milder hypercalcaemia and smaller tumours. Whilst previous research has shown that glands size can affect ioPTH kinetics in patients with multiple gland disease, the dynamics of ioPTH in patients with mild hyperparathyroidism (HPT) has not been studied. We therefore investigated the relationship between biochemical parameters and parathyroid adenoma weight, and determined the dynamics and accuracy of ioPTH assay in patients with milder hypercalcaemia undergoing parathyroidectomy.

**Methods** Patients undergoing parathyroidectomy for single gland disease from January 2004 to March 2011 were divided prospectively into two groups according to preoperative serum calcium: patients with a preoperative calcium  $\geq 2.85$  mmol/L (11.4 mg/dL) and  $< 2.85$  mmol/L were grouped as severe and mild hypercalcaemia, respectively. Correlation coefficients were calculated to assess the relationship between biochemical markers of calcium homeostasis and ioPTH measurements with respect to parathyroid gland weight.

**Results** There was a weak correlation of preoperative serum calcium ( $r=0.248$ ,  $r=0.207$ ), PTH ( $r=0.392$ ,  $r=0.275$ ), and baseline ioPTH ( $r=0.516$ ,  $r=0.244$ ) with parathyroid gland weight in severe ( $n=113$ ) and mild groups ( $n=190$ ), respectively. No correlation between the magnitude in ioPTH drop with parathyroid gland weight at 5 or 10 min post-excision

for either group was observed. Success rates (post-operative normocalcaemia) were similar for each group (99.1 % severe, 98.9 % mild).

**Conclusion** This prospective study provides evidence that ioPTH assay is a valuable tool in predicting adequate tissue removal in patients with milder and more severe hypercalcaemia due to single gland primary HPT.

**Keywords** Hypercalcaemia · Hyperparathyroidism · Intraoperative parathyroid hormone · Parathyroidectomy

## Introduction

Primary hyperparathyroidism (HPT) is a common endocrine disorder with an incidence of around 3/1,000 in Europe [1]. Most (80–85 %) cases are due to a solitary parathyroid adenoma [2–4] with excision of the pathological gland resulting in cure. Surgery carried out by bilateral neck exploration was and still is used with success rates of 90–95 % [5] when performed by experienced surgeons. A move to targeted minimally invasive unilateral parathyroidectomy (PTX) has now been permitted by the accuracy of preoperative localisation techniques such as sestamibi scintigraphy (MIBI) and high-resolution ultrasound (US) that have been shown to have a sensitivity in excess of 95 % [6] when the scan findings are concordant.

Intraoperative parathyroid hormone (ioPTH) can be used as an adjunct to preoperative localisation techniques enabling the surgeon to predict the adequate removal of hyperfunctioning parathyroid gland(s) in 94–98 % of cases [7, 8]. Furthermore, ioPTH has been shown to be an accurate predictor of post-operative success [9, 10]. Limiting to a unilateral neck exploration as opposed to a more invasive bilateral exploration, particularly when used in conjunction with preoperative localisation, reduces operation time and post-operative hypercalcaemia [11–13] and may also reduce

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cost [14]. During PTX PTH samples are assayed at baseline, pre-excision and 5 and 10 min post-excision. Results can be available to the surgeon in as little as 8 min depending on the assay used [15]. Many surgeons use the Miami criteria whereby a 50 % reduction from the highest of either the baseline or pre-excision ioPTH value predicts adequate excision of hyperfunctioning parathyroid tissue [16].

According to NIH guidelines for parathyroid surgery, a corrected serum plasma calcium equal or greater than 2.85 mmol/L (11.4 mg/dL) is the recommended threshold for PTX in patients with asymptomatic primary hyperparathyroidism [0.25 mmol/L (1 mg/dL) above the upper limit of the normal reference range] [17]. Patients with serum calcium less than 2.85 mmol/L could be considered to have a milder form of hypercalcaemia.

It is recognised that patients currently undergoing PTX for HPT may have a milder form of hypercalcaemia compared with the past [18]. Given that several studies have shown that biochemical values such as preoperative serum calcium and PTH levels correlate with parathyroid gland weight [3, 19–24], it follows that patients with milder hypercalcaemia are more likely to have smaller tumours. Previous research has also demonstrated that the size of the abnormal gland may influence the operative pattern of PTH decay [25]. Therefore in patients with milder hypercalcaemia, smaller adenoma size could potentially influence the kinetics of ioPTH: an aspect that has not previously been investigated. We were therefore interested to determine if there was a difference in the dynamics of ioPTH for patients with milder hypercalcaemia and indeed whether ioPTH was less or equally reliable for patients with mild HPT.

## Materials and methods

This was a prospective study of patients undergoing PTX for single gland disease from January 2004 to March 2011 at a tertiary centre. Once a decision to operate was made, patients underwent a neck US and a MIBI scintiscan. Clinical, biochemical and radiology data were prospectively entered into a database for all patients undergoing parathyroid surgery. A

focused approach, in which only the targeted glands were inspected, was used when either study was positive. A bilateral approach was employed when (a) localisation was negative, (b) no tumour was found or (c) no drop in ioPTH at 10 min was recorded. The highest recorded preoperative corrected serum calcium and PTH concentrations were used. For ioPTH; samples were taken at baseline, pre-excision, 5 and 10 min post-excision using a two-site chemiluminescent assay (Cambridge Diagnostics Ltd, Galway, Ireland). The percentage reduction in ioPTH at 5 and 10 min post-excision was calculated from the highest of either baseline or pre-excision values. A 50 % reduction was used as a predictor of adequate excision of hyperfunctioning parathyroid tissue [16]. False-positive results occur when ioPTH decreases by >50 % despite all hyperfunctioning gland(s) not being removed. False-negative results occur when ioPTH fails to decrease by >50 % despite adequate removal of the hyperfunctioning gland(s).

A total of 482 patients with primary HPT underwent surgery during this time period in our unit. We excluded 90 patients for whom ioPTH was either not used or the data were incomplete. Patients with parathyroid carcinoma ( $n=1$ ), MEN-1 ( $n=2$ ) and those with missing data: no recorded preoperative corrected calcium ( $n=1$ ) adenoma weight ( $n=4$ ), and 3 month post-operative corrected serum calcium ( $n=18$ ) were also excluded from the study. Patients were divided into two groups according to the preoperative corrected calcium level: group A with a preoperative calcium  $\geq 2.85$  mmol/L (11.4 mg/dL) and group B with a preoperative calcium  $< 2.85$  mmol/L. More than one gland was excised in 63 of the remaining 366 patients, 43 (17.8 %) in group A and 20 (14.4 %) in group B. Patients in whom more than one gland was excised were also excluded leaving a cohort of 303 patients (group A,  $n=113$ ; group B,  $n=190$ ). We also recognise that a cut-off at 2.85 mmol/L (11.4 mg/dL) might seem too high nowadays. It was chosen according to NIH criteria in the absence of a standard definition of ‘mild’ HPT. However to allow application of these data to wider clinical setting, we performed further analysis for a lower cut-off of 2.75 mmol/L (11 mg/dL).

The correlation between parathyroid gland weight and preoperative serum calcium levels, preoperative PTH levels,

**Table 1** Baseline variables and median ioPTH values for groups A and B

Variable	Group A ( $n=113$ )	Group B ( $n=190$ )	<i>P</i> value
Sex:			
Female ( $n=242$ )	85	157	–
Male ( $n=61$ )	28	33	–
Median age (years) (range)	64 (18–89)	64 (29–88)	0.946
Median preoperative calcium (mmol/L) (range)	2.97 (2.85–4.45)	2.72 (2.28–2.84)	<0.001
Median adenoma weight (mg) (range)	870 (100–12,000)	430 (10–5,300)	<0.001
Median preoperative PTH (pmol/L) (range)	17.1 (2.3–101.6)	11.0 (2.8–74.9)	<0.001
Median baseline ioPTH (pmol/L) (range)	25.4 (9.3–126.0)	17.3 (4.1–88.2)	<0.001

**Table 2** Characteristics of localisation scans and operation in groups A and B

	All patients % (number/total)	Group A % (number/total)	Group B % (number/total)	P value (Chi square test)
Correct localisation	79.0 (237/300)	85 (94/111)	76 (143/189)	0.01
Concordant localisation	57 (167/298)	64 (70/109)	51 (97/189)	0.03
UNE	80.0 (241/300)	86.4 (89/103)	80.0 (152/190)	0.17

UNE unilateral neck exploration

baseline PTH levels, the absolute PTH reduction and the PTH percentage reduction during surgery were calculated with Pearson's correlation. Pearson's Chi squared test was used to assess statistical difference between localisation results and the Mann–Whitney *U* test was used for baseline variables. All statistical analysis was carried out using SPSS 18.0.

## Results

The baseline variables for groups A and B are shown in Table 1. Most patients ( $n=298$ ; 98 %) underwent both US and MIBI scans (Table 2). Three patients (0.9 %) had no localisation. There is a significant difference between the rate of successful localisation and concordance between the two groups; overall, 79 % of patients were correctly localised by at least one scan (group A, 85 %; group B, 76 %) ( $P=0.05$ ) and the overall rate of concordant scans was 57 % (group A, 64 %; group B, 51 %) ( $P<0.05$ ). The accuracy of concordant scans was 97.7 %. Unilateral neck exploration was undertaken in a greater proportion of patients in group A (86 %) compared with group B (80 %).

The median parathyroid gland weight of [severe] group A (870 mg) was over double that of the [mild] group B (430 mg) ( $P<0.001$ ). Preoperative calcium and parathyroid gland weight showed a weak positive correlation in group A ( $r=0.248$ ) and group B ( $r=0.207$ ). Preoperative PTH levels also showed a weak positive correlation with parathyroid gland weight in group A ( $r=0.392$ ), group B ( $r=0.275$ ) as well as baseline ioPTH group A ( $r=0.516$ ) and group B ( $r=0.244$ ).

The per-operative pattern of ioPTH is remarkably similar for each group (Fig. 1). There was no statistically significant

correlation between parathyroid gland weight and percentage reduction in ioPTH at either 5 or 10 min in either the severe or mild groups, although absolute reduction in ioPTH at 5 and 10 min showed a weak correlation in both groups (Table 3). The overall success rate for surgery (defined as normocalcaemia at 3 months) was 99.0 %; 99.1 % in group A and 98.9 % in group B. The 1 % ( $n=3$ ) of patients with persistent hypercalcaemia had very mild hypercalcaemia [3-month post-operative corrected calcium=2.61 ( $n=1$ )–2.62 ( $n=2$ )]. For all patients, ioPTH correctly predicted cure in 291 (96 %; positive predictive value 99.3 %). The false-positive rate was 0.7 % ( $n=2$ ) and was the same in both groups (0.3 %;  $n=1$ ). The false-negative rate was 2.9 % ( $n=9$ ) and was lower in group A (1.8 %;  $n=2$ ) compared with group B (3.8 %;  $n=7$ ), leading to nine unnecessary conversions to a BNE.

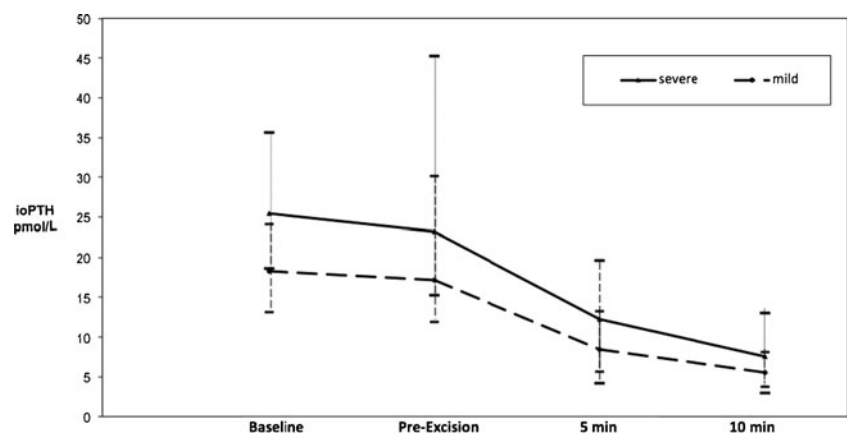
Further analysis for a lower cut-off of 2.75 mmol/L (11 mg/dL) is displayed in Table 4. No correlation existed between parathyroid gland weight and ioPTH percentage reduction in either group at 5 min. At 10 min, a weak correlation between adenoma weight and ioPTH percentage reduction was observed in the mild ( $r=0.191$ ) and severe group ( $r=0.180$ ).

Although renal function influences biochemical parameters, there was no difference in renal function between the two groups in terms of creatinine levels (data not shown).

## Discussion

In this study, the median parathyroid gland weight of [severe] group A (870 mg) was over double that of the [mild]

**Fig. 1** ioPTH kinetics in patients with severe (group A) and mild (group B) hypercalcaemia (median and interquartile range)



**Table 3** Correlation of parathyroid gland weight with absolute and percentage reduction in ioPTH at 5 and 10 min

	Group A (n=113)	Group B (n=190)
Correlation coefficient ( <i>r</i> ): parathyroid weight and absolute 5 min reduction (pmol/L)	0.321	0.169
Correlation coefficient ( <i>r</i> ): parathyroid weight and absolute 10 min reduction (pmol/L)	0.295	0.165
Correlation coefficient ( <i>r</i> ): Parathyroid weight and 5 min percentage reduction	0.074	0.070
Correlation coefficient ( <i>r</i> ): Parathyroid weight and 5 min percentage reduction	0.019	0.073

group B (430 mg) suggesting that tumour weight influences preoperative serum calcium and serum PTH levels. This is the most likely explanation for the significantly lower success rate of localisation in the milder group as it is known that accuracy of localisation drops as the weight of the gland falls [26]. This together with a significantly lower proportion of concordant scans infers that ioPTH may be more valuable for patients with mild hypercalcaemia.

The findings of this study showed no correlation between parathyroid gland weight and ioPTH percentage reduction in either group. Two previous studies have investigated the correlation between parathyroid gland weight and percentage reduction in ioPTH. Biertho et al. found no correlation between parathyroid gland weight and ioPTH percentage reduction [24] whereas Moretz et al. reported a weak negative correlation between parathyroid gland weight and percentage reduction at 10 min [23].

The similar success (normocalcaemia) rates and weak of correlation between adenoma weight and ioPTH percentage reduction between the two groups suggest that the kinetics of ioPTH and other biochemical values are similar irrespective of the tumour mass. We chose to analyse only those patients with single adenoma in

order to simplify the interpretation of tumour weight as well as minimise the confounding issues regarding the dynamics of ioPTH in patients with multiple gland disease where high false-positive rates are experienced [27]. Furthermore, previous research on the kinetics of ioPTH in patients with MEN-1 has suggested that the size of the abnormal gland may influence the operative pattern of PTH decay [25]. All patients were followed up for a minimum 3-month period, and although the focus of this paper is the intraoperative dynamics of PTH, we acknowledge that the weakness of our study is the short follow-up period to be certain of biochemical cure.

The effectiveness of ioPTH in severe and mild hypercalcaemia has not previously been reported. The definition of ‘mid HPT’ is complex and we selected serum calcium as an objective surrogate variable to define this. In the absence of an agreed standard definition, we chose a cut-off from the consensus guidelines. However, nowadays, a cut-off of 2.85 mmol/L seems too high, and to allow application of these data to wider clinical setting, we performed further analysis for a lower cut-off of 2.75 mmol/L (11 mg/dL) (Table 4). We found that there was no correlation between parathyroid gland weight and ioPTH percentage reduction in either group at 5 min. At 10 min, a weak correlation between adenoma weight and ioPTH percentage reduction was observed in the mild ( $r=0.191$ ) and severe groups ( $r=0.180$ ). This sub-analysis provides further reassurance that ioPTH kinetics are similar in patients with milder as well as more severe hypercalcaemia.

Our results provide new evidence supporting the value of ioPTH in patients with mild primary HPT. This is in line with the results of the Scandinavian audit which showed that ioPTH favourably influenced the outcome of parathyroidectomy in patients with smaller tumours [28].

**Table 4** Characteristics of patients separated with a cut-off at 2.75 mmol/L and correlation of parathyroid gland weight with percentage reduction in ioPTH at 5 and 10 min

	Calcium $\geq 2.75$ mmol/l	Calcium $< 2.75$ mmol/l
Number	185	118
Median age (year) (range)	64 (18–89)	64 (31–88)
Median preoperative calcium (mmol/L)	2.89	2.68
Median preoperative PTH (pmol/L)(range)	31.6 (2.3–101.6)	11.0 (2.8–66.9)
% reduction PTH at 5 min (range)	63 % (8.0–90.0)	58 % (–2.7–96.1)
% reduction PTH at 10 min (range)	75 % (3.0–97.0)	72 % (10.2–97.6)
Correlation coefficient ( <i>r</i> ): parathyroid weight and 5 min percentage reduction	0.059 ( $P=0.429$ )	0.180 ( $P=0.051$ )
Correlation coefficient ( <i>r</i> ): parathyroid weight and 10 min percentage reduction	0.001 ( $P=0.437$ )	0.191

## Conclusion

The absence of any difference in the dynamics of iPTH with mild and severe hypercalcaemia and equivalent normocalcaemia rates in each group provides reassurance that iPTH measurement is a valuable tool for patients with milder hypercalcaemia.

**Conflicts of interest** None.

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