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SHORT COMMUNICATION

Intraoperative parathyroid hormone testing in primary hyperparathyroidism surgery: time for giving up?

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Abstract

Purpose Intraoperative PTH testing (IOPTH) in treatment of primary hyperparathyroidism (PH) is debated. Some authors advise against IOPTH in patients with concordant preoperative imaging undergoing focused parathyroidectomy. This study aims to compare focused parathyroidectomy success rates with and without IOPTH in patients with concordant preoperative imaging.

Methods Retrospective cohort study involving 599 consecutive patients underwent surgery for PH from 2012 to 2017. Patients with discordant preoperative imaging were excluded. 426 patients underwent focused parathyroidectomy (214 patients without IOPTH and 212 with IOPTH) and were considered for the statistical analysis. In case of insufficient IOPTH decay (less than 50%), a bilateral exploration was carried out.

Results The IOPTH group and the non-IOPTH group were similar for demographics and preoperative PTH and calcaemia. 413 patients were cured and disease persistence rates between groups were not significantly different ($p > 0.05$).

Conclusions Although further testing and randomized-controlled trials are required to validate our findings, our data show that IOPTH does not seem to improve the outcome in patients with concordant preoperative imaging undergoing focused parathyroidectomy.

Keywords PTH level · Primary hyperparathyroidism · Parathyroid hormone · Parathyroidectomy · Minimally invasive surgery

Introduction

Since its introduction in clinical practice, intraoperative level of parathormone (IOPTH) has changed the attitude towards minimally invasive parathyroidectomy (MIP) in patients affected by primary hyperparathyroidism [1].

Many criteria have been proposed to assess surgical cure using IOPTH, with different sensitivity for predicting successful outcomes and detecting multiglandular disease [2].

The Vienna criterion requires a PTH drop of 50% at 10 min from gland resection from the baseline PTH sample acquired before incision [3]. The Miami criterion uses both preincision and preexcision PTH levels drawn after manipulation of the gland. A postexcision PTH drop greater than 50% from either the highest preincision or preexcision level at 10 min denotes a successful operation [4]. The even stricter Rome criterion also requires the normalization of PTH level at 20-min postexcision, and/or a PTH level 7.5 pg/l lower than the 10-min postexcision level [5].

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Nevertheless, some authors debate the IOPTH role in treating primary hyperparathyroidism, given it is not 100% accurate and requires an experienced surgeons' interpretation.

False negatives lead to an unnecessary bilateral exploration on the search for additional hyperfunctioning glands, while false positives are exposed to disease persistence. Some authors suggest giving up intraoperative level in patients with concordant preoperative imaging studies undergoing focused surgery in favour of first postoperative day PTH level [6].

Our hypothesis is that IOPTH, despite being a reliable tool in primary hyperparathyroidism surgery, does not improve success rate in patients with concordant preoperative imaging. This study, therefore, aims to compare the success rate of focused parathyroidectomy with and without IOPTH in a retrospective cohort of patients with concordant preoperative imaging.

Materials and methods

All research presented in this paper has been conducted in full accordance with the ethical principles and the Helsinki Declaration. Patients/caregiver gave informed consent about retrospective use of their data and to surgical procedures. Given its retrospective nature, the study was granted exemption from the IRB of participating institutions.

This is a retrospective cohort study involving 599 consecutive patients with normal renal function, operated for sporadic primary hyperparathyroidism, at four endocrine surgery units in Milan from January 2012 to December 2017. Patients were diagnosed with sporadic primary hyperparathyroidism according to these criteria: elevated total serum calcium, elevated total serum PTH, and normal to elevated 24-h urine calcium excretion in the presence of normal 25-OH Vitamin D levels (thus allowing ruling out familial hypercalcemic hypocalciuria patients).

Preoperatively, all the patients were submitted to neck ultrasonography and MIBI nuclear scanning. Imaging techniques were considered concordant if both detected a single gland on the same side of the neck. Patients with discordant imaging were excluded from the study (183 patients). The remaining patients underwent surgery in one of the four participating institutions. Since two of the institutions routinely performs IOPTH, while the other two do not, patients could be assigned to 1 of 2 groups: 214 (50.2%) patients underwent surgery without IOPTH (group 1) and 212 (49.8%) with IOPTH according to the Vienna criterion (group 2). There was no selection bias for assigning patients to one of the four participating institution or, consequentially, to either study group.

Intact PTH (iPTH) levels and serum calcium levels were measured preoperatively and on the first postoperative day. Preoperative exams also included 25OH vitamin D evaluation. Calcium was analyzed using the NM-BAPTA method by the system Elecsys 2010 Modular analytics E170 COBAS 702 (Roche Diagnostics GmbH, Mannheim, Germany) and results are expressed in mmoles/litre (mmol/l) (normal range 2.125–2.55). iPTH was analyzed, in central laboratory, using a sandwich electrochemiluminescence immunoassay (ECLIA) by Elecsys 2010 Modular Analytics E170 COBAS 602 (Roche Diagnostics GmbH, Mannheim, Germany) and results are expressed in picograms/litre (pg/l) (normal range 10–65). Serum 25-hydroxyvitamin D (25OH-VD) level was measured by radioimmunoassay (Liason, Diasorin, Saluggia, Italy) and results are expressed in nanograms/millilitre (ng/ml) (normal range 30.0–100.0).

All the surgical procedures were performed by the experienced endocrine surgeons. All parathyroidectomies were carried out with an MIP with a focused approach to the single abnormal parathyroid gland seen on preoperative imaging, either by open approach, with an incision smaller than 2.5 cm, or video assisted.

In patients undergoing IOPTH monitoring, blood samples for iPTH level were collected in the operating room from a peripheral vein, according to Vienna criterion, before skin incision (baseline) and 10 min after the removal of the suspicious gland [3]. IOPTH decline was defined according to Carter and Howanitz [7]. To minimize the risk of unnecessary bilateral explorations, in addition to the Vienna criterion rules, in cases with inadequate (less than 50%) decay at 10-min postexcision, another sample 35 min after excision was driven. If the decay was still below 50% from baseline, the procedure was converted into a bilateral exploration.

Patients undergoing focused surgery were discharged the day after surgery with oral calcium supplementation if they were hypocalcaemic. All of them received instructions on how to identify the symptoms of hypocalcaemia. Those submitted to conversion were discharged on the second postoperative day.

Follow-up was accomplished by office visits and iPTH and calcium measurements at 1 and 6 months after surgery. Disease persistence was defined as hypercalcaemia in setting of a high or not appropriately suppressed iPTH within 6 months after surgery.

Data were analyzed on SPSS Version 20.0 (IBM Corporation. Armonk, NY. US). The tests were two-sided, and a p value < 0.05 was considered statistically significant. The tests used for each individual evaluation are detailed in "Results" section.

Results

426 patients, 77 males and 344 females, mean age 61.98 ± 12.83 years, with concordant imaging underwent focused parathyroidectomy and were included in statistical analysis.

Patient demographics and laboratory test values are detailed in Table 1. There was no statistically significant difference (for tests and *p* values, see Table 1) between the two groups in terms of sex distribution, age, preoperative PTH, calcium, and 25-OH Vitamin D.

In the intraoperative PTH group, 13 (6.1%) patients did not show a PTH decline meeting the set criterion, and thus, they underwent bilateral exploration; among these patients, eight (61.5%) had multiglandular disease at final histology, in the remaining 5, no further abnormal gland was found (i.e. they underwent an unnecessary exploration). As per protocol, no patient underwent bilateral exploration in the non-IOPTH group.

IOPTH showed a 97.49% (94.23–99.18% with a 95% confidence interval) positive predictive value for the successful removal of the hyperfunctioning parathyroid gland, and a 95.28% (91.50–97.72% with a 95% confidence interval) accuracy (IOPTH results are detailed in Table 2).

There was no surgical site infection or symptomatic hypocalcemia episode in any patients and all patients could be safely discharged as planned, with the exception of a single patient in the IOPTH group who underwent reoperation for bleeding on the first day after the procedure. This patient was next dismissed on day 6, without any sequela. No patient was readmitted for complications in the 60 days following surgery. Five patients in the IOPTH group and six in the non-IOPTH group reported temporary hoarseness (i.e., lesser than a month). Among them, one patient in each group showed a persistent vocal fold palsy, most probably due to recurrent laryngeal nerve damage. All these patients underwent only a focused parathyroidectomy, not a bilateral exploration. As per protocol, no patient underwent bilateral exploration in the non-IOPTH group.

In 199/212 patients in the IOPTH group and in 206/216 patients in the non-IOPTH group, there was a definitive concordance between preoperative imaging and surgical findings (statistically non-significant difference between the two groups, $p = 0.490$, Chi-square test).

Cure rate was 96.9%, 13 patients (3.1%) experienced disease persistence; five of them belonged to IOPTH group.

Table 1 Patients' data

Variable	Value			Statistical test
	Whole sample	IOPTH group	Non-IOPTH group	
Patients' number	426	212	214	N/A
Male-to-female ratio	77:344	44:168	38:176	Chi-square, *p* 0.433
Age (year)	61.98 ± 12.83	59.99 ± 13.41	63.94 ± 11.94	*t* test for independent samples, *p* 0.257
Preop calcium (mmol/l)	2.86 ± 0.32	2.83 ± 0.36	2.88 ± 0.28	*t* test for independent samples, *p* 0.092
Preop PTH (pg/ml)	304.38 ± 516.86	299.52 ± 402.22	309.2 ± 610.51	*t* test for independent samples, *p* 0.316
Preop 25-OH Vitamin D (ng/ml)	19.34 ± 11.66	19.96 ± 11.8	18.72 ± 11.51	*t* test for independent samples, *p* 0.247
Surgical pathology outcome				
Adenoma	372 (87.3%)	183	189	Chi-square, *p* 0.535
Hyperplasia	54 (12.7%)	29	25	
Cured-to-persistence ratio	413:13	207:5	206:8	Chi-square, *p* 0.408

The table reports demographics, laboratory test values, surgical pathology data, and final outcome for all patients included in the study. In the last column, the statistical test used for comparing group 1 and 2 along with its *p* value is shown

Table 2 Definitions and results of true and false PTH decline and PTH failure

Condition	Definition	Number of patients
True PTH decline	PTH decline > 50% in a cured patient	194 (91.51%)
False PTH decline	PTH decline > 50% in a patient with disease persistence	5 (2.36%)
True PTH failure	Failure of the PTH to decline past the cutoff in a patient with disease persistence	8 (3.77%)
False PTH failure	Failure of the PTH to decline past the cutoff in a cured patient	5 (2.36%)

The table reports the definitions of both true and false PTH decline and PTH failure, as referenced in the study, and shows the number and percentage of patients in the intraoperative PTH group ($n = 212$) for each result

The difference in disease persistence between the two groups was not significant ($p=0.408$, Chi-square test). Details about IOPTH outcome are shown in Table 2, while details on the 13 patients with disease persistence are shown in Table 3.

Discussion

Approximately 85% of the patients with primary hyperparathyroidism (pHPT) have a single adenoma and excision of the affected gland is therapeutic [1]. Selective surgery using focused exploration has been implemented becoming the standard of care. Recognized benefits of MIP are a smaller incision, shorter operations, a decreased length of stay, uneventful recovery, and fewer complications [8, 9]. This technique, usually, is preceded by preoperative parathyroid localization studies aimed at identification of the hyperfunctioning gland. The main limit of focused surgery relies in lacking of direct visual feedback of having removed all the pathological tissues.

Assessment of surgical adequacy may be achieved by means of IOPTH monitoring. This procedure is based on the assumption that, when the affected gland is excised, the ensuing rapid decrease in circulating PTH levels can demonstrate biological healing [1, 10].

This enables the surgical team to end operation, if the success of surgery is confirmed, or to change surgical strategy when needed.

Over years, various protocols for IOPTH monitoring have been advised. They differ for PTH decay cut off, sampling times, and, even sampling frequency, and there is a complete lack of uniformity [3, 5, 11]. Thus, the choice of IOPTH criteria to predict operative success remains controversial.

The Florence group in 2014 suggested adding another blood sample at time of maximum manipulation and considering it as the baseline to calculate PTH decay [10].

Calo et al. and the Rome group recommended to obtain delayed measurements (20 min or more after excision), to minimize the risk of "blank" bilateral explorations and also to lower the probability of missing bilateral disease [12, 13].

In our series, eight patients (3.9%) had 10-min IOPTH higher than baseline, but the delayed result after excision, shown an adequate decay in all the cases. If we had not chosen to have an additional delayed IOPTH level, these patients would have been submitted to bilateral exploration and then turned out to be false positive.

On the other hand, in 38.5% of the patients receiving bilateral exploration, conversion was unnecessary, since no further pathological gland was found.

From these data, comes up the necessity for objective IOPTH criteria that may accurately predict successful surgery, thus obviating the need for further surgical exploration.

Due to the variability of PTH-related issues, many authors have questioned the validity of method especially in patients with concordant preoperative localization studies.

In Clerici's series, IOPTH monitoring failed to predict the presence of residual grossly enlarged parathyroid glands in 75% of the cases with multiglandular disease [14].

The group of Lille in 2005 suggested PTH level on the first postoperative day as more reliable in predicting successful parathyroidectomy than IOPTH, since 24-h PTH level reflects the biological recovery of the gland [6].

Table 3 Details on patients with disease persistence

Sex	Age at surgery (years)	Group	Preop serum calcium (mmol/l)	Preop PTH (pg/ml)	Preop 25-OH vitamin D (ng/ml)	First surgical procedure pathology outcome	Second surgical procedure pathology report	Disease recurrence after the second surgical procedure
M	42	IOPTH	2.93	294	10.95	Adenoma	Adenoma	None
F	64	IOPTH	3.05	251	13	Adenoma	Adenoma	None
F	36	IOPTH	2.58	244	11.62	Adenoma	Adenoma	None
F	81	IOPTH	3.08	236	22.38	Adenoma	Adenoma	None
F	61	IOPTH	2.83	202	19.21	Adenoma	Adenoma	None
F	61	Non-IOPTH	2.65	132	16.7	Adenoma	Adenoma	None
F	73	Non-IOPTH	2.7	171	24.3	Adenoma	Adenoma	None
M	60	Non-IOPTH	2.4	173	16.2	Adenoma	Adenoma	None
F	54	Non-IOPTH	3.65	131	10.84	Hyperplasia	Hyperplasia	None
F	85	Non-IOPTH	2.6	192	12.66	Adenoma	Adenoma	None
F	33	Non-IOPTH	2.92	283	14.97	Adenoma	Adenoma	None
F	76	Non-IOPTH	2.9	135	15.69	Adenoma	Adenoma	None
F	68	Non-IOPTH	2.7	231	15.61	Adenoma	Adenoma	None

The table reports the specific details in terms of demographics, preoperative laboratory tests, surgical pathology outcome, and final recurrence for all the 13 patients with disease persistence after the first surgical procedure. Interestingly enough, the second surgical pathology report did not change from the first procedure. All patients had, therefore, a multiglandular disease

Mihai et al. in 2007 reported similar outcomes in patients undergoing MIP with and without IOPTH monitoring [15]. Analogously, similar outcomes have also been reported in smaller case series by Nair et al [16].

In 2009, the European Society of Endocrine Surgeons published a position statement on modern techniques in pHPT surgery: addressing IOPTH level, they concluded it is of little added value provided that the patient has a preoperative localization with MIBI scan and ultrasonography concordant for single-gland disease [17]. It has to be noted also that IOPTH has been shown to have a relevant cost when used indiscriminately [18].

Our experience is similar, since the two groups in our series had a comparable persistence rate despite the use of IOPTH and intraoperative monitoring did not improve the detection rate of multiglandular disease. It has to be acknowledged though that, despite a considerable number of patients, our study is limited by its retrospective nature and a limited follow-up time. Furthermore, our data have no relevance on patients with non-concordant preoperative imaging: in these cases, IOPTH should be regarded as a powerful surgeons' ally.

Of course society guidelines or large case series are not able to settle the debate between surgeons who favour IOPTH, even with more stringent criteria [19], and those who do not. The formers employ IOPTH to maximize cure rate, thus reducing patients' stress and anesthesia-related risks; the latter prefer reducing the number of intraoperative explorations (and related surgical risks), procedure times and costs. Randomized clinical trials and meta-analysis covering all these aspects are the next goal in shaping primary hyperparathyroidism surgery.

Conclusion

According to our experience and given the presented data, we strongly suggest reconsidering the role of IOPTH monitoring when performing focused parathyroidectomy in patients with concordant preoperative ultrasonography and nuclear scanning.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interests pertaining this manuscript.

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