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ORIGINAL ARTICLE

Surgical treatment in patients with single and multiple gland primary hyperparathyroidism with the use of intraoperative parathyroid hormone monitoring: extensive single-center experience

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Abstract

Purpose To evaluate a single-center extensive experience and effectiveness in surgical treatment of primary hyperparathyroidism (pHPT) with the use of rapid intraoperative parathyroid hormone (ioPTH) monitoring in patients with single gland (SGpH) or multiple gland (MGpH) disease.

Methods This retrospective, single-center cohort study included 214 patients with pHPT treated from January 2010 to June 2017. In total, 172 patients fulfilled the inclusion criteria having at least one preoperative localization image study and measurement of ioPTH. Statistical analysis was made by the chi-square test and Student's *t* tests.

Results Of the 172 patients, 146 were women (85%) and 26 men (15%), with a mean age of 56.9 years; 153 (89%) had SGpH and 19 (11%) MGpH. The mean follow-up was 41.8 months. A total of 153 surgical procedures were performed as minimal invasive parathyroidectomy (MIP) based on a SGpH diagnosis; operative success was achieved in 150 cases (98%), according to ioPTH concentrations. The remainder (19 procedures) were performed as bilateral neck exploration (BNE) based on a MGpH diagnosis; operative success was achieved in 16 cases (84%). ioPTH correctly modified the initially planned operation in 26.3% of patients with MGpH.

Conclusions ioPTH enables the surgical treatment of patients with pHPT with focused approaches and excellent results, as it helps the surgeon to identify cases of MGpH. ioPTH adds value to cases where preoperative imaging failed to detect the affected gland or the results are inconclusive. According to the literature, its application seems to be of marginal benefit in cases in which there are two concordant preoperative imaging studies.

Keywords Intraoperative parathyroid hormone · Primary hyperparathyroidism · Single gland disease · Multiple gland disease · Surgical treatment

Introduction

In 1925, Felix Mandl, a surgeon in Vienna, performed the first parathyroidectomy in a patient with bone disease. The patient showed improvement for 6 months, but eventually developed recurrence and died a few years later. Despite this failure, it became apparent that the disease was not of bone but of parathyroid origin, that the treatment for hypercalcemia and bone disease could be the excision of an affected gland, and that there was a possibility of recurrence despite the successful removal [1]. Since then, there has been a shift from traditional bilateral neck exploration (BNE) towards minimally invasive parathyroidectomy (MIP) [2], mainly thanks to preoperative localization of the affected gland (parathyroid

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scintigraphy and high-resolution ultrasound), in combination with intraoperative parathyroid hormone (ioPTH) assessment [3–6].

MIP seems to be at least equally effective for the biochemical cure and definitive treatment of primary hyperparathyroidism (pHPT) compared to BNE, with a lower complication risk (5% versus 15–25%, respectively), in terms of better cosmetic results, less postoperative pain, less postoperative transient hypocalcemia, and fewer days of hospitalization [7–11].

The use of ioPTH in parathyroid surgery confirms the removal of all pathological tissue and identifies cases with remaining pathological tissue (MGpH). Additional applications include differentiating parathyroid from non-parathyroid tissue in fine needle aspiration (FNA) washout and indicating the correct side of the neck harboring pathological parathyroid tissue in jugular venous sampling [12–14].

The main reason for ioPTH monitoring in parathyroid surgery (to detect patients with MGpH who require a thorough BNE) has been a subject of debate [9, 12–20]. In our reference center, ioPTH monitoring is routinely applied in all patients with pHPT who require surgical treatment. Especially for patients with MGpH, stricter criteria for biochemical cure are applied: both the "> 50% drop" rule and "PTH value within normal range" are prerequisites for biochemical cure ("dual criteria"). In this way, treatment is tailored to each patient in order to optimize the surgical outcome. The present study aimed to evaluate our experience and effectiveness in surgical treatment of pHPT with the use of ioPTH.

Materials and methods

Study type This is a single-center, retrospective study of prospectively collected data from 214 consecutive patients with pHPT who were treated at the Department of Endocrine Surgery, from January 2010 to June 2017. The study had the approval of the Scientific Board of the Central Clinic of Athens. All patients gave written informed consent.

Patients pHPT diagnosis was established by the referral endocrinologist (typically, high serum calcium concentrations with borderline/low phosphorus and high PTH concentrations). Inclusion criteria were diagnosis of pHPT and at least 6 months postoperative follow-up. Exclusion criteria were secondary, tertiary, or familial pHPT, multiple endocrine neoplasia syndrome type 1 or 2 (MEN1 or MEN2), parathyroid cancer, previous neck surgery, thyroid pathology requiring surgery, pregnancy, and loss to follow-up. In total, 172 patients were eligible and included in the current study [reasons for exclusion: MEN1 ($n = 3$), simultaneous thyroidectomy ($n = 24$), malignancy ($n = 1$), and reoperation ($n = 14$)]. All demographic (age and gender) and medical (symptoms, localization tests, and pathology) characteristics were prospectively collected (Table 1).

Preoperative evaluation All patients underwent at least one preoperative localization image study (^{99m}Tc-sestamibi scintigraphy or high-resolution ultrasound of the parathyroid glands) performed by the same team of radiologists and nuclear medicine physicians. Patients with at least one positive preoperative localization study were candidates for open MIP. Laboratory tests, cardiology, and anesthesiology consultation and evaluation were performed the day before surgery. All patients underwent laryngoscopy as a routine preoperative evaluation by an experienced ear-nose-throat team.

Surgical management/ioPTH application The first blood sample was collected before the induction of anesthesia. All patients underwent surgery under general anesthesia, using intraoperative neural monitoring, performed by the same experienced team of endocrine surgeons. Focused parathyroidectomy, through a 2–3-cm midline skin incision above the sternal notch, was performed in all patients with suspected SGpH. The preoperatively localized lesion was identified, dissected, removed, and sent for frozen section examination. The ipsilateral parathyroid gland was not routinely exposed or inspected. An experienced pathologist provided a report within 25 min. The second blood sample was collected 10 min after the excision of the pathological tissue, and the ioPTH concentration was available within 20 min, while a third sample was obtained 20 min after the excision. Operative success was defined as an at least 50% drop from the preoperational PTH value. In cases of borderline results or suspected MGpH, the third sample concentrations were evaluated and a drop within normal range was required to define success or failure ("dual criteria"). In those cases where ioPTH concentrations did not decline appropriately, a BNE was performed using the same ioPTH protocol after the excision of every other pathological parathyroid gland. Patients with inconclusive or not indicative preoperative localization studies or with suspected MGpH were subjected to bilateral neck exploration using the same ioPTH protocol.

ioPTH assay All blood samples were collected in EDTA anticoagulated bottles, centrifuged immediately (at 4000 rpm for 5 min, Hettich Rotofix 32 Benchtop Centrifuge, Hettich, Germany), and placed into the analyzer (ADVIA Centaur CP Immunoassay System, Siemens Healthcare GmbH, Erlangen, Germany) with a turnaround time less than 20 min. Reference range was 8–72 pg/mL for PTH, 8.5–10.1 mg/dL for calcium, and 2.6–4.5 mg/dL for phosphorus.

Postoperative follow-up All patients stayed in hospital at least 1 day (range 1–5 days) and received a replacement supplementation dosage of oral or intravenous (IV) calcium and

Table 1 Patient characteristics and study results

Variables	Surgery outcome		*p* value
	Failure (*n* = 5, 2.9%)	Success (*n* = 167, 97.1%)	
Age (years)	62.0 ± 13.4 (45–78)	56.8 ± 12.6 (15–85)	0.365
Follow-up (months)	48.2 ± 27.9 (16–85)	41.6 ± 23.9 (6–95)	0.543
Gender			< 0.001
Male	1 (4%)	25 (96%)	
Female	4 (3%)	142 (97%)	
Clinical picture			0.045
Osteoporosis/osteopenia	3	85	
Renal disease	3	92	
Pathologic fracture	1	3	
Fatigue	5	125	
Stress/mental disorder	4	132	
Cardiovascular disease	1	10	
None	2 (40%)	18 (11%)	
Neck ultrasound			< 0.001
No localization	2 (14%)	12 (86%)	
Localization	1 (1%)	152 (99%)	
Unclear	2	1	
Not done	0	2	
SestaMIBI scan			< 0.001
No localization	2 (8%)	24 (92%)	
Localization	1 (1%)	91 (99%)	
Unclear	1	1	
Not done	1	51	
Both imaging techniques			< 0.001
Both negative	1 (17%)	5 (83%)	
Both positive	1 (1%)	85 (99%)	
Discordant	3 (4%)	77 (96%)	
Not done	0	0	
Surgery			
BNE	2 (18%)	9 (82%)	< 0.001
UNE	0 (0%)	3 (100%)	
Focused/targeted	2 (1%)	151 (99%)	< 0.001
Convention	1 (20%)	4 (80%)	0.001
Pathology			
Adenoma (SGpH)	2[a] (1%)	151 (99%)	< 0.001
Double adenoma	0 (0%)	5 (100%)	
Hyperplasia	3 (21%)	11 (79%)	
Lesion size (cm)	0.66 ± 0.32 (0.3–1.0)	1.14 ± 0.78 (0.3–5.0)	0.085

Results are given as mean ± standard deviation and/or as range (min–max) for the quantitative variables and as frequencies (%) for the categorical variables

BNE bilateral neck exploration, *SestaMIBI scan* ^{99m}Tc-Sestamibi scintigraphy, *SGpH* single gland primary hyperparathyroidism, *UNE* unilateral neck exploration, *SGD* single gland disease

[a] High concentrations of ioPTH after the removal of a single affected gland; procedures not continued due to patient's medical history ($n = 1$) and loss of recurrent laryngeal nerve signal ($n = 1$)

vitamin D, if needed. Serum PTH, calcium, and phosphorus were evaluated on the first postoperative week, the first postoperative month, the sixth postoperative month, and then on an annual basis. Biochemical cure was defined as calcium concentrations within normal range for at least 6 months postoperatively; persistent disease was defined as postoperative hypercalcemia and recurrent disease as hypercalcemia after at least 6 months of postoperative normocalcemia. Cases with persistent or recurrent disease were re-evaluated by the referral endocrinologist.

Statistical analysis Data were presented as mean ± standard deviation. The chi-square test or Student's t tests were performed for comparisons between groups. A p value of 0.05 indicated statistical significance. All data analysis was performed with R Studio - Open Source Edition (Boston, MA, USA).

Results

Patient characteristics A total of 172 patients [26 (15%) men, 146 (85%) women, mean age 56.9 ± 12.3 years] were included in this analysis, with a mean follow-up of 41.8 ± 23.3 months (range 6–95). Of them, 153 (89%) had SGpH and 19 (11%) MGpH [6 (3.5%) with double adenomas and 13 (8%) with multiple nodular hyperplasia]. Patients' demographic and medical characteristics are shown in Table 1. Biochemical cure was eventually achieved in 167 (97%) patients.

Localization studies All patients had at least one preoperative localization study (^{99m}Tc-sestamibi scintigraphy or high-resolution parathyroid ultrasound), whereas 118 underwent both. In 92 (78%) of them, there were matching results (86 positive and 6 negative in both studies). Using the pathology report as the gold standard, ^{99m}Tc-sestamibi scintigraphy successfully revealed MGpH in 5/14 patients [36% sensitivity, 50% specificity, 83% positive predictive value (PPV), 10% negative predictive value (NPV), and 38% accuracy). High-resolution ultrasonography successfully revealed MGpH in 8/17 patients (47% sensitivity, 67% specificity, 89% PPV, 18% NPV, and 50% overall accuracy). In patients with SGpH, ^{99m}Tc-sestamibi scintigraphy successfully revealed the disease in 87/105 patients (84% sensitivity, 0% specificity, 99% PPV, 0% NPV, and 83% accuracy). Ultrasonography successfully revealed SGpH in 145/151 patients (97% sensitivity, 0% specificity, 99% PPV, 0% NPV, and 96% accuracy).

Surgical procedure A total of 153 procedures were performed as MIP, following a SGpH diagnosis. Operative success was achieved in 150 cases (98%). In 19 cases diagnosed as MGpH, cure was achieved in 16 patients (84%). Of those, 11 were operated on as BNE due to preoperative localization studies (cure rate 82%); three were operated on as MIP for the same reason (cure rate 100%); and in five initially planned as MIP, the approach was modified to BNE due to failure of ioPTH to drop (cure rate 80%). Overall, according to the ioPTH results, MIP was offered to 156/172 patients (91%) (cure rate 98%). If we had relied solely on imaging studies, only 86/172 patients (50%) would have had both studies positive and, therefore, have been eligible for MIP. The cure rate, in that case, would have been 98%.

ioPTH assay The preoperative, 10 min post-excision, 20 min post-excision, and first postoperative day PTH concentrations are presented in Table 2. In the group of patients with SGpH, the cure rate was 98%. ioPTH correctly predicted biochemical cure in 150 patients, and operative failure in two cases, whereas in one case, ioPTH showed decline (false negative), from 101.3 to 68 pg/mL, 20 min after the excision (ioPTH 99% sensitivity, 100% specificity, 100% PPV, 67% NPV, and 99% accuracy).

In patients with MGpH, the cure rate was 84% (16/19 patients). ioPTH correctly predicted biochemical cure in 13 patients and also correctly predicted operative failure, in three patients. On the other hand, ioPTH dropped > 50% from the preoperative value (false negative) in 3/13 patients, while there was remaining pathological tissue (81% sensitivity, 100% specificity, 100% PPV, 50% NPV, and 84% accuracy). Characteristics of patients in whom biochemical cure was not achieved are presented in Table 3.

In 15 out of the 19 patients with MGpH, BNE was performed either as an initially planned operation or due to an unsatisfactory drop in ioPTH concentrations after the excision of the first gland. In this subgroup, ioPTH successfully predicted biochemical cure in 10 cases, failed in three, and had three false positive results (77% sensitivity, 83% PPV, and 67% accuracy). In the same subgroup, ^{99m}Tc-sestamibi successfully localized the affected glands in three cases and failed in eight (27% sensitivity, 100% PPV, and 27% accuracy). The ultrasound was successful in six patients, negative in eight, and false positive in one (43% sensitivity, 86% PPV, and 40% accuracy). Finally, in 4/15 patients (27%) with MGpH, both localization studies failed to detect the additional affected gland (73% accuracy). ioPTH correctly indicated these patients (accuracy 100%); three of them were cured, while in the fourth, the ioPTH concentrations remained high (surgical failure due to an ectopic extra-cervical lesion).

Discussion

The gold standard method in the surgical treatment of pHPT used to be BNE. This method consists of visual identification of all four parathyroid glands, intraoperative biopsy or frozen section to confirm the diagnosis, or either SGpH or MGpH. According to some authors, there is no need for preoperative localization studies to be performed and the cure rates are extremely high (> 95%) in experienced hands [19, 21–23].

Table 2 Biochemical profile of patients included in the study

Variable	All cases		SGpH		MGpH		*p* value
	Value	Drop (%)	Value	Drop (%)	Value	Drop (%)	SGpH vs. MGpH
PTH preoperative (pg/mL)	221.9 ± 219.0		227.4 ± 230.6		177.5 ± 63.6		0.350
PTH postoperative at 10 min (pg/mL)	55.4 ± 66.4	75.1	45.4 ± 55.7	80.1	135.9 ± 89.8	23.4	< 0.001
PTH postoperative at 20 min (pg/mL)	39.0 ± 62.3	82.4	29.8 ± 51.0	86.9	113.5 ± 91.4	36.1	< 0.001
PTH postoperative at 24 h (pg/mL)	27.1 ± 39.6	87.8	25.0 ± 37.1	89.2	47.5 ± 52.4	73.2	0.017
Calcium preoperative (mg/dL)	10.6 ± 0.9		10.6 ± 0.9		10.6 ± 0.8		0.780

Data are given as mean ± standard deviation. Student's *t* test was used. PTH values regarding MGpH patients refer to the initial drop after the excision of the first ("dominant") pathological gland

PTH parathyroid hormone, *SGpH* single gland disease, *MGpH* multiple gland disease

However, as patients present with mild or no symptoms, the surgical treatment of pHPT has been shifted to less extensive methods, namely, unilateral or focused approach or even MIP [8, 9, 24, 25].

Several experts declare that the use of ioPTH is the most accurate and effective adjunct tool in predicting biochemical cure in patients with pHPT who undergo focused or MIP surgery, even in cases with MGpH or discordant preoperative imaging findings. On the other hand, many researchers suggest that ioPTH adds little to pHPT surgical treatment, while increasing cost and morbidity as well as time of surgery [2, 4, 7, 12, 16, 21, 22, 26, 27]. Since patients with SGpH are usually candidates for MIP with or without ioPTH use, it remains to be determined whether this adjunct has a role in the surgical treatment of patients with MGpH.

This study evaluated the accuracy of ioPTH in predicting biochemical cure in patients with SGpH or MGpH. The overall cure rate was 97%, comparable to most series. ioPTH successfully predicted biochemical cure in 98% of patients with SGpH and 84% of patients with MGpH. Without ioPTH, the MIP approach would be safely applicable in only 50% of patients. Moreover, ioPTH use successfully modified the initially planned operation in 26.3% of MGpH patients, predicting operative success in 80% of them and revealing 20% operative failure at the same time.

Several studies are in accordance with our findings, supporting improved outcome for patients undergoing MIP with the use of ioPTH. Chen et al. demonstrated increased cure rates (from 90 to 100%, $p < 0.001$) with the use of ioPTH in patients treated with MIP. Similarly, Irvin et al. demonstrated increased cure rates in patients treated with MIP and ioPTH compared to those treated with BNE without ioPTH (from 94 to 97%, $p = 0.02$). Westerdahl and Bergenfelz state that 10% of patients who underwent initial surgery without the use of ioPTH would not have been biochemically cured. Regarding localization studies, the literature varies as well. Sugg et al. characterized ioPTH as the most reliable predictor for MGpH, while others supported its use in identifying patients with MGpH [12, 13, 16, 25, 28, 29].

On the other hand, some authors have reported that equally excellent results of MIP can be achieved by meticulous patient selection with concordant preoperative imaging studies without the use of ioPTH. Gawande et al. showed only 1% added value with the use of ioPTH in patients with concordance in scintigraphy and ultrasound results. Also, Jacobson et al. reported 97% success of MIP without ioPTH use. Stalberg et al.

Table 3 ioPTH concentrations in patients for whom biochemical cure was not achieved

id	PTH concentrations						Glands excised	MIBI Loc	US Loc
	PreOp	At 10 min (1)	At 20 min (1)	At 10 min (2)	At 20 min (2)	PostOp			
1.	211.0	232	206.0	184.0	211	168.4	2 hyperplastic	–	Unclear
2.	231.4	217.8	201.6	199.2	197.8	191.1	2 hyperplastic	Unclear	–
3.	324.1	451.4	551.7	N/A	N/A	414.3	1 adenoma	Unclear	Unclear
4.	67.5	93.2	97.8	74.5	91.3	95.5	1 adenoma/hyperplastic	–	–
5.	58.4	71.2	71.2	N/A	N/A	138.0	1 adenoma	+	+

PTH concentrations presented in picograms per milliliter. Number in brackets represents the gland excised

ioPTH intra-operative parathyroid hormone, *PreOp/PostOp* preoperative/postoperative, *PTH* parathyroid hormone, *MIBI Loc* SestaMIBI scan localized the pathological gland, *US Loc* ultrasonography localized the pathological gland, *N/A* non-applicable demonstrated that little value was added with the use of ioPTH in patients selected by scintigraphy, while others support the use of ioPTH in MIP when there is only one preoperative localization or the results of two studies are discordant [15, 18, 30]. However, it is evident that excellent results can be achieved without ioPTH only in a very selective group of patients; therefore, such a perspective would exclude subjects with pHPT from the MIP approach. Our results further support this concept, since only 50% of patients would have been eligible for the focused approach without ioPTH use.

An additional objection to the use of ioPTH is that the method shows high rates of false negative and false positive results. False negative results (up to 9%) lead to unnecessary BNE, with increased morbidity, operative time, and cost, while false positive results (up to 6%) result in operative failure and early disease recurrence. In contrast, large series of patients estimate these incidences to approximately 1–3%, stating that ioPTH failure is not a matter of assay but rather of the criteria used [30–33]. In our series, ioPTH use in patients with SGpH had 99% overall accuracy. Some authors have maintained that using the Miami criteria can reduce the false negative results but slightly increase the false positive ones, compared with the Vienna criteria. In an attempt not to miss affected glands and to obviate the need for reoperation after a surgical failure, the Vienna criteria seem to be more appropriate compared with the Miami criteria. Our results appear to support this concept [12, 31, 32, 34, 35].

The retrospective nature of our study is one of its limitations. As it is an observational study, it carries all the drawbacks of its type. The absence of a control group is another limitation. Finally, our data may be subject to selection and/or referral bias, since patients were referred to our center after a thorough evaluation by expert endocrinologists.

In conclusion, the results of this study strongly suggest that routine use ioPTH allows the surgical treatment of patients with pHPT with focused approaches and excellent results. ioPTH helps the surgeon in the timely identification of cases of missed MGpH and, thereby, to alter the initially planned strategy. ioPTH adds value to cases where preoperative imaging failed to detect the affected gland or the results are inconclusive. Its application seems to be of marginal benefit in cases where there are two concordant preoperative imaging studies. ioPTH monitoring is a valuable adjunct in the era of focused parathyroidectomy, which should be applied in patients in an individualized way, according to surgeons' experience and familiarity with the current protocols. Since there is a lack of large, randomized clinical trials, future studies should be focused in this direction in order to provide more robust conclusions along with evidence regarding the cost-effectiveness of the routine use of the method.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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