



Role of intraoperative PTH monitoring and surgical approach in primary hyperparathyroidism



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HIGHLIGHTS

- IOPTH monitoring confirmed cure during surgery.
- It influenced the surgical approach taken in those with equivocal imaging results.
- This determined extent of surgical treatment required to be considered optimum.

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ABSTRACT

Aims: The use of intraoperative PTH monitoring (IOPTH) in combination with preoperative imaging has been useful to surgeons performing minimally invasive parathyroidectomy principally for adequacy of excision. However, its role within patients with equivocal imaging remains less clear particularly regarding the reduction of bilateral neck explorations. This study investigated the influence of IOPTH monitoring on the type of surgical approach adopted for patients with primary hyperparathyroidism (PHPT). Specifically, determining its impact amongst patients with equivocal imaging results.

Methods: 165 patients undergoing parathyroidectomy for PHPT at a single institution by a single surgeon, between 2008 and 2012, were included. Patients were divided into 2 groups, IOPTH monitoring and non-IOPTH monitoring. They were sub-classified according to their imaging strengths: strongly positive, equivocal and negative imaging. The percentages of patients undergoing focused, unilateral and bilateral operations were determined.

Results: 108 patients had IOPTH monitoring and 57 patients did not based on the availability of IOPTH monitoring. Patients with strongly positive imaging had a higher frequency of focused operation in both groups; IOPTH 73.4% and non-IOPTH 71.4%. Patients with negative imaging results had a higher frequency of bilateral operations; IOPTH 77.8% and non-IOPTH 72.7%. In patients with equivocal imaging results more focused/unilateral operations were performed with IOPTH monitoring 66.6% versus non-IOPTH 25%. The use of intraoperative PTH increased the likelihood of a unilateral procedure with equivocal imaging compared to those with negative imaging $p = 0.04$.

Conclusion: IOPTH monitoring is most useful as an adjunct to preoperative imaging when imaging results are equivocal allowing for more focused/unilateral operations to be performed.

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1. Introduction

Primary hyperparathyroidism (PHPT) is due to single gland disease (SGD) in approximately 70–95% of cases, gland hyperplasia responsible for 15%, double adenoma 4% or rarely caused by parathyroid carcinoma [1,2]. Associations include familial syndromes

such as Type 1 and 2 Multiple Endocrine Neoplasia (MEN). Curative treatment is the surgical removal of pathological parathyroid glands.

Traditionally, conventional bilateral neck explorations (BNE), were used as the primary surgical approach to identify all four parathyroid glands and excise those that appeared enlarged [2]. Success was confirmed through histological frozen sections which helped to determine the nature of the parathyroid tissue and postoperative biochemical cure.

IOPTH use during surgery involves blood to be taken from a

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peripheral vein pre-incision and then again pre-excision to determine the highest level of PTH – this would be the baseline [2]. Success is defined as a fall in PTH levels of >50% at 10 min post-excision compared to baseline (Miami criteria) – with an accuracy of 97% [3,4].

This aim of this study is to investigate what influence IOPTH monitoring has on the type of surgical approach adopted for patients with PHPT. Specifically, determining its impact amongst patients with equivocal imaging results and whether the use of IOPTH modifies a surgeon's operative management of PHPT.

2. Patients and methods

165 patients who underwent surgery for PHPT between January 2008 to December 2012, by a single surgeon at St Thomas' Hospital, were included. Data was retrieved retrospectively from Electronic Patient Records (EPR) and the surgical database. Exclusion criteria were patients undergoing reoperations, MEN1, patients who underwent parathyroidectomy at another institution by the same surgeon and concomitant thyroid surgery.

IOPTH monitoring was available once a week at this institution and all patients scheduled to undergo surgery on this day received IOPTH monitoring. Patients were not intentionally selected to be operated on this day. Patients were divided into 2 groups, those that had received IOPTH monitoring during surgery (IOPTH) (and those without IOPTH monitoring (non-IOPTH) (Table 1). The patients were further subdivided according to their preoperative imaging strengths: strongly positive, equivocal and negative imaging.

Surgical procedure was based on imaging and the extent of surgery was on satisfaction that successful operation was done. Images were strongly positive if either the USS or the sestamibi scan were reported as positive or both were reported positive. Negative images were those where both USS and sestamibi were negative. If scans were formally reported as negative but to the radiologist or surgeon there was a slight suspicion of a lesion on sestamibi these were defined as equivocal images (Table 2). The percentages of patients undergoing focused, unilateral and bilateral operations were then determined. In the absence of IOPTH monitoring if cure was less certain the surgeon would do further neck exploration.

Success was defined using the Miami Criteria: a fall in PTH levels of >50% at 10 min post-excision compared to baseline which was obtained for each patient. The baseline used was the highest value obtained from either pre-incision or pre-excision. All patients were followed up 6 months post-operatively or longer if there were any concerns regarding biochemistry.

Fishers exact 2 tailed test was used to examine the associations between the patients undergoing various types of surgery and

Table 1
Demographics & surgical approach in patients with IOPTH monitoring & those without (non-IOPTH).

	IOPTH		Non-IOPTH
Total number	106		57
Female: Male (no.)	73: 33		39: 18
Mean Age (range)	56 (18–69)		52 (16–84)
	IOPTH	Non-IOPTH	Mean age IOPTH: Non-IOPTH
Focused operations number (%)	61 (57.5%)	30 (52.6%)	57.5: 53.6
Unilateral operations number (%)	19 (17.9%)	10 (17.5%)	57.7: 47.7
Bilateral operations number (%)	26 (24.5%)	17 (29.8%)	61.6: 58.4

Table 2
Strengths of imaging.

Imaging strength	Strongly positive	Equivocal	Negative
USS/sestamibi	+/+ or -/+	?/- or -/?	-/-

+ = Abnormal gland visualised ± location determined.

- = Abnormal gland not visualised ± location unclear.

? = Weak and unconvincing image.

imaging surgery in the IOPTH and non-IOPTH groups. A probability level of $p < 0.05$ was considered significant.

3. Results

Of the 165 patients, 108 patients had IOPTH monitoring and 57 patients did not. 2 IOPTH patients were excluded from analysis due to missing data. Table 3 and Fig. 1 shows patients who had strongly positive imaging results were more likely to undergo focused operations independent of IOPTH; IOPTH 73.4% and non IOPTH 71.4%. Those patients with negative imaging results had a higher percentage of patients undergoing bilateral operations; IOPTH 77.8% and non IOPTH 72.7%.

The results of using IOPTH in patients with equivocal imaging results from this study demonstrates more focused/unilateral operations being performed (67%) compared to those with negative imaging, where 4 unilateral procedures were performed (22%) ($p = 0.04$). Those with non-IOPTH are much more likely to undergo BNE (75%) in the equivocal imaging group compared to IOPTH (33.3%).

There were 5 patients whom had additional IOPTH samples taken during surgery as PTH did not drop >50% from the first samples taken. Those in the equivocal group did not require further samples to be taken although numbers were small. These 5 patients had strongly positive images; 2 of these patients underwent focused procedure whilst the remaining 3 patients had BNE. A further third IOPTH sample was required for 2 of the patients that had undergone BNE. Those with negative imaging only 1 case required a second IOPTH sample to be taken and this patient went on to have a BNE. These 4 patients who required further IOPTH samples and underwent bilateral operations had MGD. Incidence of MGD in those who had IOPTH monitoring was 20/106 (18.7%). In the non IOPTH group incidence of MGD was 12/57 (21.2%).

4. Discussion

Tibblin introduced unilateral exploration in patients with PHPT. He carried out neck exploration on one side of the neck—his study found 43/102 patients had an abnormal gland on this side [5]. This identification allowed for a unilateral parathyroidectomy to be limited to this side but 45/102 patients had a normal gland on this first side Tibblin as a result carried out an exploration on the opposite side in these selected patients only. When patients who underwent minimal exploration and unilateral procedures were compared to those whom underwent BNE lower post op complications were observed – Tibblin's work was the precursor of focused surgery.

Improving imaging and appreciation that the majority of patients have single gland disease has led to the development of unilateral and focused or minimally invasive procedures (MIP). Correct identification and complete excision of the abnormal parathyroid glands with minimal complications is the main goal of surgery.

Preoperative ultrasound combined with sestamibi scans are the localising imaging modalities of choice. Patients with negative, discordant or equivocal imaging usually undergo BNE. A small number of patients with persistent or recurrent hypercalcaemia

Table 3

Imaging strength versus type of surgery patients underwent in both groups – IOPTH and non-IOPTH.

Type of surgery	IOPTH		
	Strongly +ve n (%)	Equivocal* n (%)	Negative* n (%)
Focused	58 (73.4)	3 (33.3)	0 (0)
Unilateral	12 (15.2)	3 (33.3)	4 (22.2)*
Bilateral	9 (11.4)	3 (33.3)	14 (77.8)
Total number	79	9	18

* $p=0.04$ Fishers Exact 2 tailed n = number of patients

Type of surgery	non-IOPTH		
	Strongly +ve n (%)	Equivocal n (%)	Negative n (%)
Focused	30 (71.4)	0 (0)	0 (0)
Unilateral	6 (14.3)	1 (25)	3 (27.3)
Bilateral	6 (14.3)	3 (75)	8 (72.7)
Total number	42	4	11

require re-operation. Ectopic glands, multiglandular disease (MGD), difficulties in differentiating between hyperplastic and adenomatous glands on histology and incomplete excision of hyperplastic tissue may have been responsible for persistent hypercalcaemia and therefore failure of parathyroidectomy.

The use of intraoperative PTH monitoring (IOPTH) in combination with preoperative imaging has been useful to surgeons in performing minimally invasive parathyroidectomy (MIP). Previous studies report MIP to be linked with better cosmetic results from a smaller incision, quicker operative time, uneventful recovery and a reduced risk of developing hypocalcaemia and recurrent laryngeal nerve injury [6].

The results of this study suggest that IOPTH may play a significant role in influencing the type of surgical procedure performed in patients who have equivocal imaging results. Traditionally these patients in our study would have been treated with BNE in a manner similar to negatively imaged patients.

There is a lot of controversy regarding the use of IOPTH. Suliburk et al. (2011) [7] examined all MIP that took place at a single institution over a 10 year period – they found that 98% of MIP were successful without the use of IOPTH. Padma et al. (2013) [8] found that the confirmation by IOPTH use changed the surgical management in 66% of images which were equivocal and 29% were the imaging was positive.

Our results agree with the study carried out by Lew et al. (2008) [9] where they demonstrated that operative management was changed with the use of IOPTH in 74% of patients with equivocal preoperative imaging. The use of IOPTH allowed 66% of these patients to undergo a less invasive unilateral neck exploration. We demonstrated that patients with equivocal imaging results are more likely to undergo focused/unilateral operations when IOPTH is used than without it. This significant reduction in BNE means quicker operative time and reassures surgeon he has

adequately excised abnormal parathyroid in equivocal cases without extending neck exploration. Hence, determines extent of surgical treatment required to be considered optimum.

It is evident that patients are more likely to undergo focused operations if the preoperative images are strongly positive in both IOPTH and non-IOPTH groups-independent of the use of IOPTH. This was previously demonstrated by Sebag et al. (2003) [10] – patients who had two concordant images had a single gland disease and IOPTH did not add anything to the surgical management for these patients. Those patients with negative imaging are more likely to undergo bilateral operations. These results suggest imaging has a significant role on type of surgical approach used. It can therefore be argued that the use of IOPTH has a less important role in those with strongly positive or negative imaging with regards to the surgical approach used.

Our study confirms that the drop of PTH <50% suggests MGD and hence BNE was necessary to identify the extra foci and further (2nd or 3rd) IOPTH measurements were beneficial to help determine success. A recent prospective study [11] concluded that IOPTH showing a decay of >50% at 5 min signifies success avoiding the need to take samples at 10 and 15 min which could potentially reduce operative time further.

Lee et al. (2014) [12] looked at the rate of failure with the use of IOPTH; 96.6% of patients were successfully treated at 13 months post-surgery. Of the 3.4% of failed surgery – the most common cause of this was the surgeon not detecting all the abnormal glands in MGD. In 63.6% (7/11) of these cases the surgeon did not proceed to BNE despite inadequate fall in IOPTH – in these cases the preoperative images demonstrated a single gland disease [12]. They also stopped the surgery earlier in order to keep the anaesthetic time minimal. In this study patients who had a fall of IOPTH of greater than 70% from baseline all had a successful parathyroidectomy whereas those that had a fall in IOPTH of 50–59% had

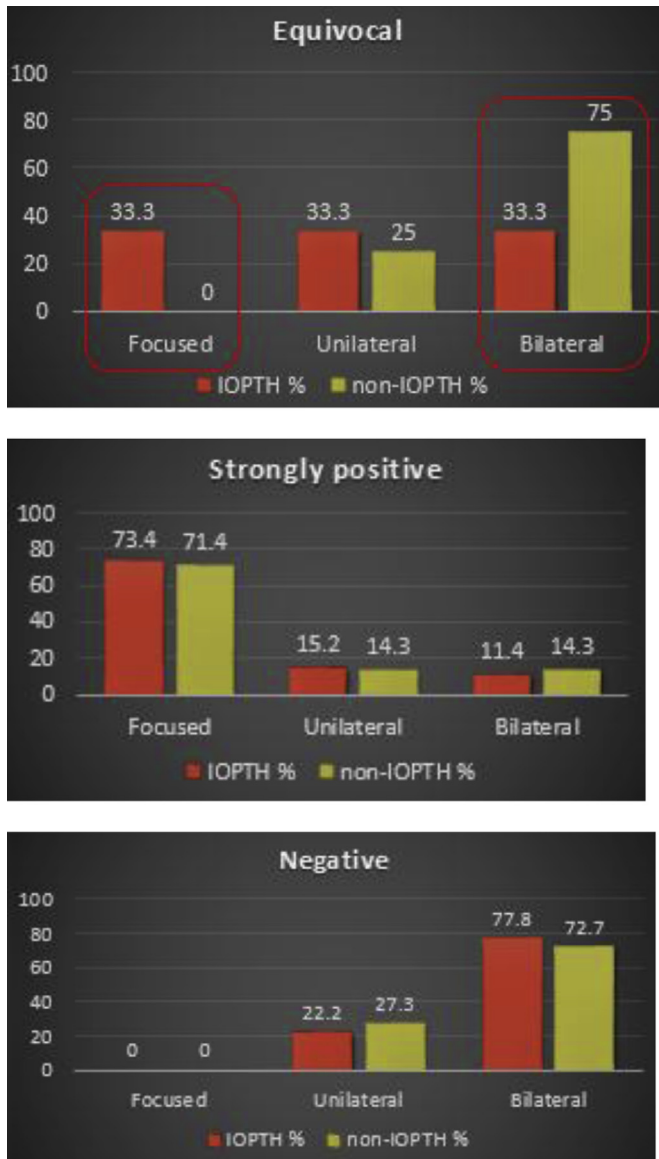


Fig. 1. Graphs to show imaging strength vs. type of surgery in IOPTH & non-IOPTH group.

a failure rate of 20% and they have suggested for these patients it is important for the surgeon to use his/her own judgement and clinical skills to decide whether to proceed to BNE [12].

The study by Lew & Irvin (3rd) (2009) [13] examines the 10-year outcome of a focused parathyroidectomy in 164 patients with PHPT using IOPTH. They found that IOPTH use is successful with regards to limited scarring; it does not increase the recurrence rate when normal parathyroid glands are left intact with no failure in detecting MGD. Of note there was no difference in cure rates in patients whom underwent UNE or BNE.

All patients were followed up post operatively at 6 months and further follow up only if there were further concerns about biochemistry otherwise patients were discharge back to their Endocrinologists for follow up due to the distance they travelled. During follow up a number of patients lost to follow up. 18/56 patients were lost to follow up in the non-IOPTH monitoring group whilst 14/106 patients in the IOPTH group. A number of patients did require a longer duration of follow up to ensure biochemical parameters remained normal. The postoperative complications were

minimal in both groups. One patient developed pseudomonas wound infection and five patients continued to have borderline elevated PTH in the context of low vitamin D levels but normal calcium levels and provided with a one year follow up in the IOPTH group. Otherwise, there were no further complications and no vocal cord palsies.

The limitations of this study include are it is a retrospective study looking at a single surgeon's opinion as documented in pre-operative correspondence and operating notes and from formal radiology reports at a single institution. A number of patients being lost to follow up.

5. Conclusion

MIP is now most commonly used as the surgical treatment for primary hyperparathyroidism compared to the traditional BNE. This study has shown that IOPTH monitoring is most useful as an adjunct to preoperative imaging when imaging results are equivocal allowing for more focused operations to be performed in this group of patients. The use of IOPTH monitoring can provide vital information within minutes to help determine the extent of surgical treatment required to be considered optimum; especially in patients with MGD. We can therefore recommend the use of IOPTH in patients with equivocal imaging results.

Disclosures

None.

Ethical approval

None.

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None.

Author contribution

All authors named involved with data collection. A. A. Khan and J. G. Hubbard designed concept for the study. A. A. Khan and J. G. Hubbard provided data analysis and interpretations, drafting of the manuscript and critical revision of manuscript and final approval to submit the manuscript.

Conflicts of interest

None.

Guarantor

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