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The utility of the radionuclide probe in parathyroidectomy for primary hyperparathyroidism

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ABSTRACT

INTRODUCTION Parathyroidectomy is the definitive treatment for primary hyperparathyroidism but the intraoperative identification of adenomas is challenging. The aim of this study was to evaluate the utility of a radionuclide probe (RNP) in addition to intraoperative parathyroid hormone (IOPTH) measurement as an intraoperative diagnostic adjunct in patients undergoing parathyroidectomy for primary hyperparathyroidism.

METHODS This was a retrospective cohort study of patients treated between 2004 and 2015 in a university affiliated teaching hospital. Patients were grouped into those with RNP use (RNP+) and those without (RNP-). The primary outcome measure was rate of operative failure, which included false positives. The diagnostic sensitivity and positive predictive value of both RNP and IOPTH were also evaluated.

RESULTS A total of 298 patients were included in the study, 127 (42.6%) being in the RNP+ group and 171 (57.4%) in the RNP- group. The false positive rate for the RNP+ patients was 1.6% compared with 9.4% for RNP- patients (p=0.006, hazard ratio [HR]: 6.45). The rates of operative failure were 6.3% and 11.7% respectively (p=0.159, HR: 1.97). RNP use had a sensitivity of 92.0% and a positive predictive value of 98.3% compared with 78.6% and 95.2% respectively for IOPTH monitoring.

CONCLUSIONS RNP use is associated with fewer false positives and reduced operative failure than IOPTH measurement. It also has a higher sensitivity and positive predictive value. RNP use is recommended in centres that have the required facilities.

KEYWORDS

Parathyroidectomy – Parathyroid neoplasm – Intraoperative care – Sensitivity

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Primary hyperparathyroidism (pHPT) is a common endocrine disorder with a prevalence of 0.21–2.2%.[1] It is caused by autonomous hypersecretion of parathyroid hormone in one or more parathyroid glands resulting in hypercalcaemia.[2] If left untreated, it may lead to clinical symptoms such as accelerated bone loss, renal stones, fatigue, depression and cardiovascular disease.[3]

Parathyroidectomy is the only definitive treatment for pHPT; its success is largely aided by positive preoperative imaging for localisation and excellent intraoperative tests to confirm adequate resection.[4] Although sestamibi scintigraphy or ultrasonography of the neck can been employed preoperatively to assist in surgical resection, their sensitivities in detecting parathyroid adenomas are limited. In one study, a combination of sestamibi imaging and ultrasonography of the neck only achieved a sensitivity of 88%.[5] Consequently, it is clear that other intraoperative tests are necessary as adjuncts to surgery to optimise patient outcome.

The introduction of intraoperative parathyroid hormone (IOPTH) monitoring and a well defined criterion for successful exploration proposed by Irvin *et al* revolutionised parathyroid surgery in the 1990s,[6] prompting many surgeons to adopt focused parathyroidectomy.[7,8] IOPTH has a sensitivity of 80–95% but is still associated with false positives.[9,10] Furthermore, Siperstein *et al* reported a potential 16% failure rate in a large cohort of patients undergoing focused parathyroidectomy despite concordant sestamibi imaging and IOPTH measurement.[11] Others report fluctuation including increases in IOPTH levels following parathyroidectomy.[12] This discrepancy may be due to intraoperative manipulation of the parathyroid glands and may result in diagnostic uncertainty if IOPTH testing was the sole intraoperative diagnostic adjunct.

The radionuclide probe (RNP), on the other hand, is safe and associated with a 94% success rate in patients undergoing parathyroidectomy.[13] In patients with pHPT, RNPs may be used as a valuable adjunct to surgery to reduce the risk of operative failure, which (although rare) remains a major problem as repeat surgery is often more difficult, with greater risk of complications. The aim of this study was to

evaluate the benefit of RNP use in addition to IOPTH measurement as an intraoperative diagnostic adjunct in patients undergoing parathyroidectomy for pHPT.

Methods

This was a retrospective cohort study utilising a prospectively maintained database in Cork University Hospital, a large university affiliated tertiary referral centre in Ireland. Ethical approval for the study was obtained from the clinical research ethics committee at University College Cork. All adult patients undergoing parathyroidectomy for pHPT between 2004 and 2015 were included. Patients on lithium therapy, those with less than 30 days of follow-up and those with missing data were excluded as these confound the assessment of operative failure.

In our practice, all patients scheduled for parathyroidectomy undergo sestamibi scintigraphy for preoperative localisation and IOPTH measurement as an intraoperative diagnostic adjunct. If imaging is undertaken on the day of surgery, the RNP is employed intraoperatively as an additional diagnostic adjunct using Norman's 20% rule.[14] Minimally invasive surgery is performed if scintigraphy localisation is successful and open exploration beginning at the lower pole of the left thyroid lobe is performed otherwise. When a grossly enlarged gland suspicious for parathyroid adenoma is encountered and resected, and if the diagnosis is supported by intraoperative adjuncts, the operation is considered successful and does not proceed to a full four-gland exploration.

Our hypothesis was that RNP use is associated with fewer false positives and greater diagnostic sensitivity. In order to test this, patients were divided into two groups: those with RNP use (RNP+) and those without (RNP-). The primary outcome measure was operative failure, which included false positives. These were defined as intraoperative diagnosis of parathyroid adenoma without this being the case on histopathology and disease persistence or recurrence during the follow-up period. Additionally, the sensitivity and positive predictive value (PPV) of each modality was calculated. Data were analysed using Student's t-test, Fisher's exact test and the chi-squared test where appropriate with the aid of SPSS® version 22 (IBM, New York, US) and Prism® version 6 (GraphPad Software, La Jolla , CA, US). All p-values were derived from two-tailed tests and a p-value of <0.05 was considered statistically significant.

Results

A total of 298 patients were included in the study, 127 (42.6%) being in the RNP+ group and 171 (57.4%) in the RNP- group. Differences in patient demographics, serum biochemistry and adenoma characteristics did not achieve statistical significance with the exception of estimated glomerular filtration rate, and initial and final corrected calcium (Table 1). pHPT was more prevalent in female patients in both cohorts, outnumbering male patients by four to one. Most patients were on the older side of middle age and the average follow-up duration was one year. Adenomas were most commonly located at the lower pole of the left thyroid lobe, followed by the lower pole of the right lobe. Seven cases of single adenomas were identified without documented locations. Among the single adenomas, 1.0% were found in ectopic locations and the incidence of multiglandular disease (MGD) including four-gland hyperplasia was 7.4%.

There were no significant differences between the groups in terms of IOPTH results. The overall rate of operative failure was 9.4%: 6.3% in cases with RNP use and 11.7% in cases without. The hazard ratio was 1.97 in favour of RNP use but owing to the rarity of this event, this failed to reach statistical significance (p=0.159). The overall rate of false positives was 6.0%: 1.6% in cases with RNP use and 9.4% in cases without. The hazard ratio was 6.45 in favour of RNP use and this difference was statistically significant despite its rarity (p=0.006). These outcomes are presented in Table 1. The sensitivity and PPV for each intraoperative diagnostic adjunct was also evaluated. The sensitivity of the RNP was 92.0% compared with 78.6% for IOPTH while the PPV was 98.3% and 95.2% respectively.

Discussion

Intraoperative diagnosis of parathyroid adenomas can be challenging. Our results show that patients in the RNP+ group had a lower rate of false positives than those in the RNP- group. This translated to a lower rate of operative failure for RNP+ patients. This is explained by its high sensitivity and PPV, which allows it to better identify resected diseased glands than IOPTH measurement. Radionuclide administered for sestamibi scintigraphy is taken up by both thyroid and parathyroid tissue but is washed out of thyroid tissue relatively rapidly, allowing for the interpretation of the imaging. By the time the patient is brought to theatre, only diseased parathyroid tissue retains more than 20% of radioactivity compared with background levels, as described by the Norman group.[14]

As both scintigraphy and RNP results are dependent on radionuclide uptake by diseased glands, some may argue that RNP use shares the weakness of sestamibi imaging in the identification of MGD (including parathyroid hyperplasia). However, in studies of parathyroid hyperplasia secondary to chronic renal disease, RNP use was shown to retain its utility and improve the success of surgery.[15,16] We believe RNP should behave similarly for parathyroid hyperplasia in pHPT. In a study of 845 patients treated with focused parathyroidectomy guided by IOPTH monitoring, the authors concluded that it was the inability of the surgeon to find the abnormal parathyroid gland (rather than missed MGD) that led to operative failure.[17]

We propose that RNP use be paired with IOPTH measurement; IOPTH levels may not drop appropriately in cases of MGD, which should prompt further exploration in which the RNP has utility in identifying disease. Our results support this as there was no significant difference in rates of MGD between the RNP+ and RNP- groups. A total of 22 patients had MGD; 6 of these were in the RNP+ cohort. In five of the six RNP+ cases, ex vivo counts were greater than 20% of

Table 1 Comparison of variables for cases with and without RNP use

	RNP+ (*n*=127)	RNP- (*n*=171)	*p*-value
Demographics			
Male	27 (21.3%)	31 (18.1%)	0.555
Female	100 (78.7%)	140 (81.9%)	
Mean age (years)	60.7 (SEM: 1.3)	62.4 (SEM: 1.1)	0.314
Mean eGFR (ml/min/1.73m^2)	71.7 (SEM: 1.8)	79.0 (SEM: 1.9)	**0.008**
Mean follow-up duration (months)	12.3 (SEM: 0.8)	12.1 (SEM: 0.8)	0.870
Biochemistry			
Mean initial PTH (pg/ml)	150 (SEM: 9.7)	138 (SEM: 9.6)	0.397
Mean initial calcium (mmol/l)	2.84 (SEM: 0.02)	2.78 (SEM: 0.02)	**0.013**
Mean final calcium (mmol/l)	2.43 (SEM: 0.02)	2.37 (SEM: 0.01)	**0.004**
Adenoma size			
Mean diameter (cm)	1.91 (SEM: 0.07)	1.78 (SEM: 0.07)	0.213
Mean weight (g)	1.17 (SEM: 0.11)	1.07 (SEM: 0.13)	0.564
Adenoma location			
Left lobe, upper pole	24 (18.9%)	19 (11.1%)	0.336
Left lobe, lower pole	42 (33.1%)	44 (25.7%)	
Right lobe, upper pole	15 (11.8%)	26 (15.2%)	
Right lobe, lower pole	35 (27.6%)	43 (25.1%)	
Unknown	2 (1.6%)	5 (2.9%)	
Ectopic	1 (0.8%)	2 (1.2%)	
Multiglandular disease	6 (4.7%)	16 (9.4%)	0.179
Outcome			
Intraoperative PTH drop >50%	100 (78.7%)	131 (76.6%)	0.677
No adenoma	2 (1.6%)	16 (9.4%)	**0.006** (HR: 6.45)
Operative failure	8 (6.3%)	20 (11.7%)	0.159 (HR: 1.97)

eGFR = estimated glomerular filtration rate ; HR = hazard ratio; PTH = parathyroid hormone; RNP = radionuclide probe; SEM = standard error of means

background. In contrast, IOPTH levels failed to drop appropriately for 11 of the 22 patients after resection of their glands.

RNP use is safe and quick as it involves no intervention beyond placing the RNP first over the thyroid bed to obtain a background reading and then again over the resected tissue. There is a risk of false positives in the case of concomitant thyroid disease, such as an undiagnosed follicular thyroid adenoma.[18] Nevertheless, our results show that these cases are rare and are usually apparent on gross examination by the operating surgeon.

At the other end of the spectrum, there is a risk of false negatives, most commonly if surgery is delayed too long after administration of the radionuclide. This risk can be alleviated by performing surgery within 3.5 hours of sestamibi scintigraphy, as described by the Norman group.[14] In our experience, therefore, the primary downside of this technique is the difficulty in logistics (organising imaging on the day of surgery, allowing time for its interpretation by radiology colleagues and then having the patient ready for the operation within 3.5 hours of the imaging).

While the two cohorts in this study were evenly matched for most variables tested, renal function was worse in the RNP+ group, and these patients also had higher initial and final corrected calcium levels. Differences in renal function may influence calcium homeostasis. However, in the absence of other evidence of kidney disease, a glomerular filtration rate of >60ml/min/1.73m^2 is considered normal and the means of both groups were well above this. We argue that although statistically significant, the difference in renal function would be clinically negligible.

Likewise, the mean initial corrected calcium values for both cohort groups were well over the upper limit of normal and the final corrected calcium values were well below this

Table 2 Diagnosis of adenoma using a radionuclide probe or IOPTH measurement compared with histology report results

	Positive histology	Negative histology	
Ex/in vivo counts >20%	115	2	Sensitivity: 92.0% PPV: 98.3%
Ex/in vivo counts <20%	10	0	
IOPTH drop >50%	220	11	Sensitivity: 78.6% PPV: 95.2%
IOPTH drop <50%	60	7	

IOPTH = intraoperative parathyroid hormone; PPV = positive predictive value

limit. Two-way analysis of variance was performed to evaluate any difference in the drop in serum calcium postoperatively between the groups but there was no statistically significant difference (p=0.970). Furthermore, if these differences in calcium levels and renal function had any clinical significance, they should have resulted in an increase in operative failure for RNP+ patients but in the fact the opposite was the case.

Finally, a potential criticism of our study is our lack of data on complication rates. The only difference in the management of each group was the use of the RNP, which has been demonstrated to be safe. In a series of 1,650 patients (with half undergoing open exploration and half focused parathyroidectomy), the overall complication rate was 2%.[19] It is reasonable to conclude that parathyroidectomy is relatively safe and given our small numbers, any difference in complication rates would have no statistical significance.

Conclusions

The RNP is simple and easy to use, reduces the risk of false positives and overall operative failure, and increases diagnostic sensitivity. Despite RNP use in parathyroidectomy being described over a decade ago, it may be underutilised because of the success of IOPTH measurement. However, RNP use has benefit when employed in conjunction with IOPTH monitoring and the RNP should be used in every centre with the required facilities for the best patient outcome.

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