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Research Article

The Importance of Level of Drop of Intra-operative Parathyroid Hormone in Predicting Recurrence After Parathyroidectomy for Primary Hyperparathyroidism

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Abstract

Background: During parathyroidectomy for hyperparathyroidism, intraoperative parathyroid hormone (IOPTH) levels are used to confirm excision of parathyroid adenoma. A drop in IOPTH level of 50% or drop to a normal level is associated with a high cure rate. However, there are still a number of patients who fit this criterion who have recurrent hyperparathyroidism. The authors hypothesize that a drop in PTH to a level below 4 pmol/l (37.72 pg/mL) rather than just a 50% drop would decrease the rate of recurrence disease.

Methods: The authors conducted a retrospective review of consecutive patients who underwent surgery for parathyroid adenoma between March 2015 and December 2018. Parathyroidectomy was performed with curative parathyroidectomy defined as drop in IOPTH below 4 pmol/l (37.72 pg/mL) after 10-15minutes from excision (2-3 half-life periods of PTH) of abnormal Parathyroid gland.

Results: 72 patients were identified who underwent Parathyroidectomy for primary hyperparathyroidism during the study period. Post resection IOPTH levels below 4 pmol/l correctly predicted an operative success rate near 100% in the cohort. Contrarily IOPTH level drop more than 50% but above a level of 4 pmol/l (9 cases) was associated with an additional unidentified Parathyroid adenoma in 7 cases.

Conclusions: Post parathyroidectomy drop in IOPTH level below 4 pmol/l appears to be more predictive of successful treatment for primary hyperparathyroidism related to parathyroid adenoma compared to standard criteria.

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Keywords: Parathyroid; Parathyroidectomy; Primary hyperparathyroidism; Endocrine disorders.

Introduction

Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders. It is the third most common clinical endocrine disorder after diabetes and thyroid disease, with prevalence between 0.1-1.0% and an incidence of approximately 28 cases per 100,000 individuals in the general population. SPHPT occurrence is three times more in women than men and parathyroid adenoma occurs 85-90% of SPHPT. Primary hyperparathyroidism is the unregulated overproduction of parathyroid hormone (PTH) resulting in abnormal calcium homeostasis. In approximately 85% of cases, primary hyperparathyroidism is caused by a single adenoma. In 15% of cases, multiple glands are involved (i.e., either multiple adenomas or hyperplasia). Rarely, primary hyperparathyroidism is caused by parathyroid carcinoma [1-4]. Parathyroidectomy is the definitive treatment for primary hyperparathyroidism. Minimally invasive parathyroidectomy (MIP) focuses on a targeted, unilateral neck exploration with removal of the hyper functioning adenoma. This approach relies on preoperative and intraoperative localization of an adenoma [5].

Currently, there are several perioperative adjuncts that can facilitate the MIP approach and increase its success rate. The most commonly utilized intraoperative adjunct is IOPTH (intraoperative parathyroid hormone) monitoring [6]. The analysis focused on PTH (parathyroid hormone) levels for the success of curative surgery. The doctors took blood samples: prior to skin incision (baseline) on day of surgery and another sample was drawn 10-15 min (2 to 3 half-life cycles of PTH) after resection of the hyper functioning gland to analyze the drop in PTH levels [7]. The authors followed the standard criteria for curative resection which is a drop of ≥50% from baseline of IOPTH or decrease of IOPTH to the normal range (normal range 1.9 to 6.9 pmol/L [17.9-65.1 pr/ml]). This is associated with an over 91% cure rate. The authors hypothesize that a more significant drop in PTH to a level below 4 pmol/l (37.72 pg/ml) would decrease the rate of missed adenoma in comparison to standard criteria. The results were compared between ≥50% drop from baseline of PTH at 10-15 min post-resection of hyper functioning gland and focusing on drop of IOPTH below 4 pmol/l (normal range 1.9 to 7.9) regardless of PTH levels prior to skin incision [8].

Methodology

This retrospective study included 72 patients diagnosed with primary hyperparathyroidism. Patients were selected on the basis of consecutive sampling who underwent parathyroidectomy for a parathyroid adenoma at Cleveland Clinic Abu Dhabi, between March 2015 and December 2018. There were 21 men and 51 women. The patients were between the age groups of below 50 years to more than 50 years. Pre-operative site determinations of glands were done through ultrasound and nuclear scan to assist with planning for minimally invasive parathyroidectomy [9]. A PTH base line blood sample was taken on the day of surgery prior to the patient going into OR. A

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parathyroidectomy was performed, and specimen sent for histopathology and during surgery an IOPTH level was taken about 10-15 minutes after the suspected parathyroid adenoma was removed. Curative parathyroidectomy was defined as drop in IOPTH below 4 pmol/l after 5 minutes from excision and was compared to standard criteria of a drop of IoPTH ≥ 50% from baseline or IOPTH decrease to the normal range (normal range 1.9 to 6.9 pmol/l [17.9-65.1 pr/ml]) but above 4 pmol/l [10,11]. Basic statistics were performed using Microsoft Excel software. 4D-CT scan was done for all the patients for identifying parathyroid glands for doing the parathyroid surgery. Iodine based dye was given intravenously to have a clear imaging. Images were acquired when the contrast was maximum in the glands. 4D-CT scan is the latest technology for parathyroid imaging, and it gives a better imaging. The 4D-CT showed parathyroid adenoma in all patients planned for surgery. The study was approved by the institutional review board (IRB).

Results

There were 29 percent male and 71 percent female. Age wise 6 percent were below fifty years, 17 percent were 50-59 years, 21 percent were 60-69 years while 56 percent were seventy years or more. All 72 patients had a drop in IOPTH level of more than 50% but 9 of the patients had levels above 4 pmol/l (12.5%). The patients were followed up periodically. After six months follow up 4 patients (all male) were found to have additional adenomas. These three patients were noted to have persistent/recurrent primary hyperparathyroidism on follow up. All the three patients were found to have missed adenomas on the second operation which were removed successfully. All three were men of age 60 years and above. The preoperative calcium range was 8.5 to 12.5 mg/dl while the post operative patients became hypocalcaemic having the calcium range 4.7 to 6. There was a rise in IOPTH level within ten to fifteen minutes after the operations. After the operation none of the patients had any additional hyper functioning glands. All patients fell below >50% of the elevated value within 10 to 15 minutes. This speaks for the success of the operations. The remaining 63 patients achieved a drop of PTH below 4pmol/l and this was curative. Hence, drop in PTH levels post resection of parathyroid adenoma below 4pmol/l correctly predicted the curative operation success rate 87.5%. Calcium supplement was prescribed to all patients due to the hypocalceamic condition.

	Gender (total 72)		Age (total 72)			
	Male	**Female**	**<50 yrs**	**50-59 yrs**	**60-69 yrs**	**70 yrs and above**
No (n=72)	21	51	4	12	15	41
Percentage	29	71	6	17	21	56

Table 1: Demographic information.

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		Gender	Age	Parathyroidectomy done for primary hyperparathyroidism	>50% decrease of PTH within 10-15min	>50% decrease of PTH but PTH above 4 pmol/l	Number of patients found with a second adenoma intra-operatively	Number of patient re-operated and re-explored with a missed adenoma
N	Valid	72	72	72	72	72	72	72
	Missing	0	0	0	0	0	0	0
Mean		1.7083	3.2917	1	1	1.875	1.9444	1.9583
Median		2	4	1	1	2	2	2
Mode		2	4	1	1	2	2	2
Std. Deviation		0.45772	0.94104	0	0	0.33304	0.23067	0.20123

Table 2: Statistics.

>50% decrease of PTH		>50% decrease of PTH but PTH above 4 pmol/l		Patients found with missed adenoma		Patients re-operated with a missed adenoma	
No	Percent	No	Percent	No	Percent	No	Percent
72	100	9	12.5	4	6	3	4

Table 3: Parathyroidectomy done for primary hyperparathyroidism (n=72).

Discussion

Currently, the success rate of parathyroidectomy is greater than 95% in centers experienced in this procedure and complications are rare [12]. Intraoperative PTH monitoring is an important adjunct to detect multiglandular disease in patients undergoing minimally invasive surgery for primary hyperparathyroidism. Pitfalls may occur due to technical assay problems or blood sampling errors [13]. The high incidence of parathyroid adenoma as a cause of primary hyperparathyroidism (85% to 96%) [14], short half-life (5 min) of parathyroid hormone along with remaining suppressed functioning of normal parathyroid glands, allows the measurement of IOPTH to evaluate its decline rate after excision of hyper functioning parathyroid tissue [15]. The currently accepted Vienna criteria for measurement of IOPTH describes a decrease in PTH of 50% or more from preincision (base line) value within 10-

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15minutes following excision of hyper functioning parathyroid gland excision. This defines surgical cure (91%) and predicts post-operative normo calcemia [16].

To perform intraoperative PTH monitoring during parathyroid surgery, blood samples are collected at a predetermined time interval (10-15 minutes)-post excision of abnormal parathyroid gland.

This is done by the anesthesiologist (via an established peripheral venous or arterial line) or the surgeon (via a needle puncture of the internal jugular vein, anterior jugular vein, or external jugular vein in the operative field) [17]. For each sample, 3 to 5 mL of whole blood is collected in an ethylenediamine tetraacetic acid (EDTA) tube. It is important to avoid hemolysis during blood collection by filling the EDTA tube completely and avoiding any shaking of the sample. Blood samples are then sent for PTH assay, the results of which are interpreted according to one of the intraoperative PTH monitoring protocols [18].

The authors followed the dual criteria protocol for PTH assessment. Dual criteria protocol-widely used method for PTH monitoring, the dual criterion protocol, requires a minimum of two samples (the pre-skin-incision sample and a post-gland-excision sample). The first sample is obtained preincision on the day of surgery. The second blood sample is collected from the same site 10-15 minutes after excision of a suspected adenoma [19]. During this study focus was changed from a 50% drop or normalization in PTH to drop in IOPTH below 4 pmol/l (37.72 pg/mL) to define curative surgery for Primary hyperparathyroidism. This study evaluates the PTH levels before and after the surgery done for primary hyperparathyroidism. As per previous studies a drop in IOPTH more than 50% (compared to baseline level) 10-15 minutes after excision of parathyroid adenoma is defined as curative surgery [20]. In this study the authors used a drop in IOPTH below 4 pmol/l of (normal level 1.9 pmol/l-6.9 pmol/l) to define curative surgery for primary hyperparathyroidism due to adenomas rather than standard criteria. The authors found 9 patients in this study who had a drop in IOPTH more than 50% from baseline levels, but the PTH was above 4 pmol/l, which led the authors to explore the remaining parathyroid glands. Among these 9 patients it was found that 7 of the patients had an additional parathyroid adenoma. After excision of additional adenomas in those 7 patients, PTH levels dropped below 4 pmol/l, which supports the definition of curative surgery for primary hyperparathyroidism.

Conclusion

In this approach with the measurement of IOPTH levels below 4 pmol/l 10-15 minutes post abnormal parathyroid gland excision made it possible for the authors to reduce the incidence of missing additional parathyroid adenomas in patients undergoing minimally invasive parathyroidectomy and subsequent need for re-exploration. The decrease in PTH level below 4 pmol/l post parathyroid excision seems to play a key role in the correct determination of surgical outcome, strongly improving the possibility of performing correct patient treatment and redefining these criteria for curative surgery for primary hyperparathyroidism.

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