



Split Central Venous Sampling of Parathyroid Hormone in Non-localizing Parathyroid Tumors

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Abstract

One-hundred-and-fifteen patients underwent neck exploration for hyperparathyroidism at the Keck School of Medicine, University of Southern California. Twenty-seven of these patients had intraoperative parathyroid hormone levels drawn simultaneously from both internal jugular veins and received a definitive diagnosis of their disease based on tissue pathology. This majority of these diagnoses were comprised of parathyroid adenomas or multiglandular (four-gland) hyperplasia. From this cohort, thirteen cases had parathyroid abnormalities that could not be localized by technetium-99 sestamibi scan, while six patients received imaging results that conflicted between sestamibi scan and high resolution neck ultrasonography or sestamibi scan and 4D CT scan. By utilizing the split venous sampling technique, we demonstrate that the hormone gradient between the left and right internal jugular veins is a statistically valid predictor of the side and the etiology of a parathyroid abnormality. This holds true even in instances where patients receive non-localizing or conflicting preoperative imaging results. The accuracy of this technique improves dramatically as the absolute value of the gradient exceeds 100 pg/ml. Split vein parathyroid hormone sampling is a useful adjunct in guiding parathyroid surgery when conventional imaging modalities are inadequate. Application of this technique provides the surgeon a greater degree of assurance that a minimally invasive approach will result in an appropriate cure.

Introduction

Split Central Venous Sampling of Parathyroid Hormone in Non-localizing Parathyroid Tumors. Parathyroid surgery has improved tremendously since the adoption of intraoperative parathyroid hormone (IO-PTH) monitoring in 1990 by Yves Chapuis and George Irvin as an adjunct to preoperative parathyroid imaging [1,2]. Steady advances in diagnostic radiology and biochemical analysis continue to increase the yield and efficiency of intraoperative PTH assessment so that focused neck exploration can be performed with minimal risk of overlooking residual or multiglandular disease. In its current state, the technetium-99m sestamibi scan accurately localizes hyper functional tissue in 71% - 79% of patients with a single adenoma [3]. Single adenomas account for 85% - 97% of documented hyperparathyroidism – with multi-glandular hyperplasia (2.5% - 15%) and carcinoma (1%) forming the remainder of cases [4]. Coupling sestamibi technology with four-dimensional Computed Tomography (4D CT) and neck ultrasonography demonstrably improves sensitivity to 79% - 95% [5]. Still, there remain instances when preoperative imaging is inconclusive or in

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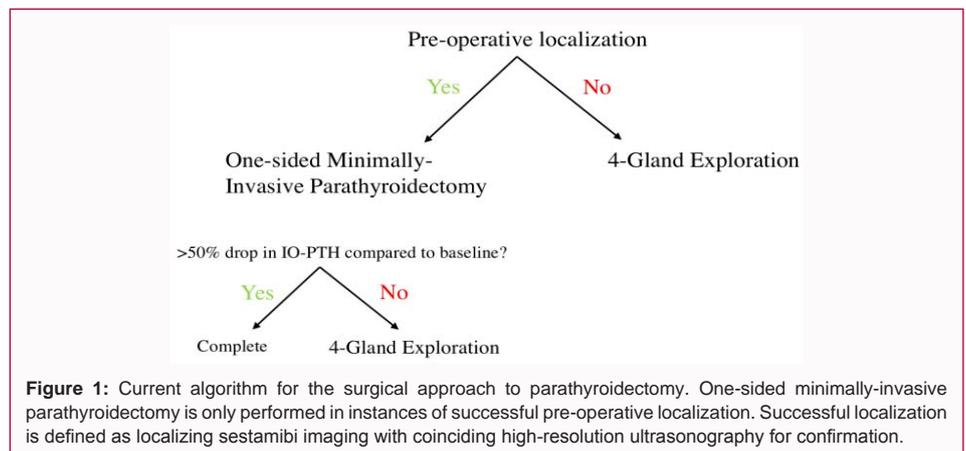


Figure 1: Current algorithm for the surgical approach to parathyroidectomy. One-sided minimally-invasive parathyroidectomy is only performed in instances of successful pre-operative localization. Successful localization is defined as localizing sestamibi imaging with coinciding high-resolution ultrasonography for confirmation.

conflict amongst the different modalities. The conventional algorithm for parathyroidectomy is outlined in Figure 1. One-sided minimally-invasive parathyroidectomy is performed when disease is localized preoperatively. Otherwise, patients with inconclusive localization are treated with bilateral exploration of the four parathyroid glands. In a previous study, we demonstrated that intraoperative split Internal Jugular Vein (IJV) PTH values can be used to inform the surgeon of laterality in situations where preoperative imaging is unable to localize parathyroid abnormalities [6]. That study abided by the Mayo protocol, where a >50% reduction compared to baseline peripheral PTH levels 10 or more minutes after careful exploration and resection was considered to be biochemically curative. In the face of non-localizing or conflicting preoperative imaging studies, the author maintains the value in employing this split internal jugular vein PTH sampling technique as an aid to determine the etiology and laterality of parathyroid disease. This study evaluates the continued efforts of a single institution to use this method.

Materials and Methods

Participants

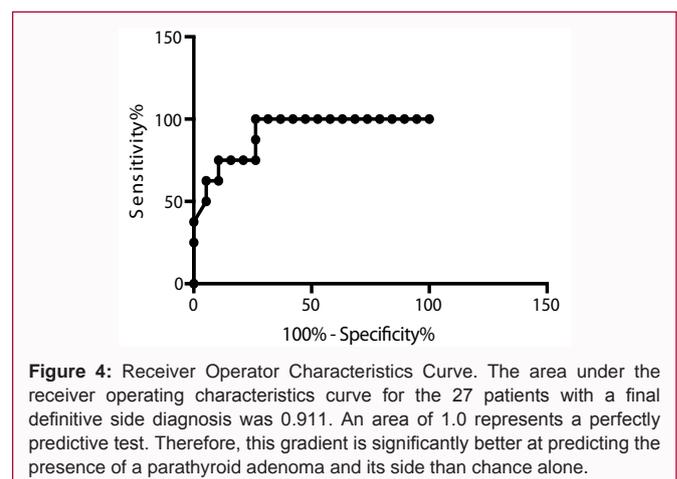
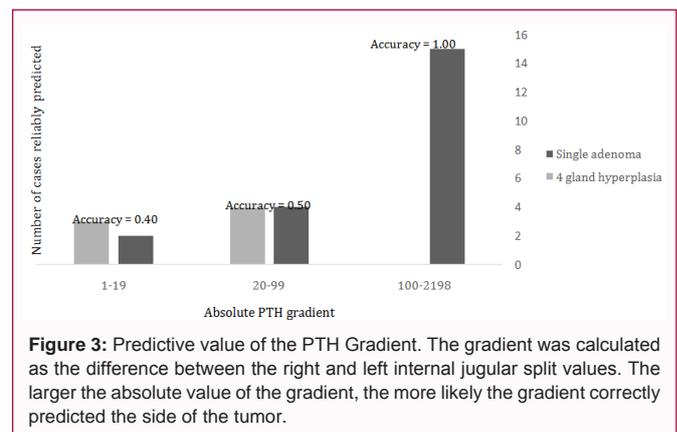
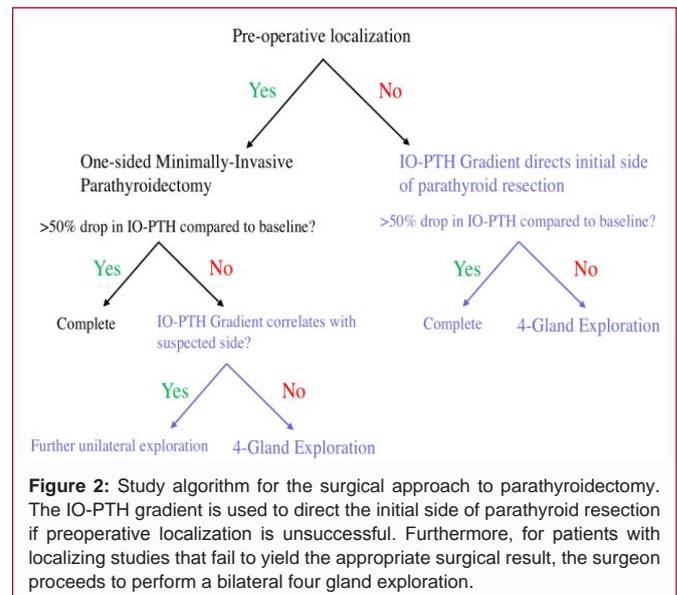
One hundred and fifteen patients underwent neck exploration for hyperparathyroidism at the Keck School of Medicine of the University of Southern California between January 2010 to May 2016 (excluding 2012). A cohort of 41 individuals had intraoperative PTH levels drawn from both jugular veins, which represents the protocol in question aimed at minimizing the extent of surgery and determining the ability of increased PTH levels to correlate with the side of the adenoma. Patients with secondary hyperparathyroidism (5) or parathyroid cancer (1) were excluded from the study. Patients without a final pathologic diagnosis (3) and/or without PTH levels drawn from both left and right internal jugular veins were also excluded. Revision surgical cases were discounted as well (1). The medical records of all patients were reviewed retrospectively in accordance with the regulations and practices formulated by the Health Sciences Institutional Review Board.

Procedure

Samples drawn for the patient intraoperatively were immediately analyzed by a technologist with the immunochemiluminescence assay (Future Diagnostics, Wijdien, The Netherlands). The peripheral vein sample obtained after induction of general anesthesia served as the baseline preoperative PTH level. For each patient, the left and right internal jugular vein samples were compared for gradients. Preoperative localization studies with technetium-99-sestamibi scintigraphy were used to evaluate for abnormal parathyroid tissue. These results were confirmed with high-resolution neck ultrasonography. 4D CT was used in select patients. In certain cases, sestamibi scans were non-localizing. The split internal jugular vein PTH gradients were used to direct the initial area of surgical exploration. In all cases, suspicious gland removal was followed by IO-PTH sampling from a peripheral vein 10 minutes later. Repeated failure of the PTH levels to drop >50% from the baseline value after careful unilateral exploration resulted in a bilateral 4-gland exploration and redrawing of PTH levels until the criteria was satisfied (Figure 2).

Statistical methods

The p-values for the difference in PTH between the right and left internal jugular veins were calculated by use of paired sample t tests stratified by location and pathologic tissue confirmation. The p values for difference in right and left internal jugular veins by localization and



side were calculated with independent sample t tests. Sensitivities and specificities were generated by comparing gradients which correctly predicted etiology and side versus those that were incorrect (Figure 3 and 4). P-values for comparing the proportion of non-localizing studies between this study and the previous study were calculated by the use of a z-test. Statistical analysis was performed with GraphPad Prism version 7.0 (GraphPad Software). Statistical significance was defined as $P < 0.05$.

Table 1: Patients with hyperparathyroidism.

	Localizing (n=31)	Non localizing (n=13)
Adenomas	27 (87%)	6 (46%)
Hyperplasia	4 (13%)	7 (54%)

Results

After applying the selection criteria, 27 patients had undergone surgery with bilaterally-drawn internal jugular vein PTH samples and received a definitive pathologic diagnosis to correlate with the intraoperative findings. Thirteen of these patients had non-localizing technetium-99-sestamibi scans and 6 cases had conflicting preoperative imaging. Table 1 and 2 illustrates the patients that had localizing or non-localizing scans and the etiology of their disease. Table 3 shows the means and standard deviations of intraoperative internal jugular PTH samples. It demonstrates that left-sided adenomas are significantly more likely to have higher left-sided PTH values while right-sided adenomas are significantly more likely to have high-right sided PTH values. There is no statistically significant relationship between 4-gland hyperplasia patients and their left or right-sided PTH values. Overall, an increase in right-sided IJV PTH values correlated with right-sided adenomas and an increase in left-sided IJV PTH values correlated with left-sided adenomas. Of the 20 patients that had a single adenoma, the PTH gradient was correct in predicting the adenoma's side in 19 cases. Graph 3 represents the accuracy of this sampling technique: the greater the absolute value of the gradient between the left and right IJ samples, the more likely the gradient was predictive of tumor side. For patients with a PTH gradient 100 and above, both the presence of a unilateral adenoma and its respective side was predicted with 100% accuracy. Below this threshold, the ability of the gradient to predict side and etiology begins to diminish. The area under the receiver operating characteristics (ROC) curve in Figure 2 represents the ability of this gradient to discriminate between a lateralized adenoma on the correct side against adenomas on the wrong side or multiglandular disease. An area of 0.5 implies that the test has no predictive value, while an area of 1.0 signifies a perfectly predictive test. The area under ROC curve was 0.911, indicating that the gradient is substantially better at distinguishing tumor side than chance alone.

Discussion

Since publishing our first report in 2011, the standard for IO-PTH monitoring in parathyroid surgery has remained largely unchanged. IO-PTH levels drawn 10-minutes after excision that decrease more than 50% when compared to baseline levels are widely accepted as an indicator of operative success. In that time, our institution has been gathering additional data to best inform surgical decision-making especially when preoperative sestamibi scintigraphy is unreliable. When inadequate localization occurs, ectopic adenomas, multiglandular disease or imaging limitations must be considered. We demonstrate here that a PTH gradient

Table 2: Internal jugular vein PTH values in patients with pathologic confirmation.

Adenoma Side	No.	Mean RIJ	RIJ SD	Mean LIJ	LIJ SD	P value (RIJ VS LIJ)
L	9	148.00	148.00	657.78	621.68	0.012
R	11	574.63	706.11	185.64	101.07	0.034
4	7	188.57	75.76	212.00	75.03	0.13
P value (L v R)		0.038		0.027		
Total	27					

Table 3: Predictive value of the PTH Gradient.

Gradient	Single Adenoma	4 Gland Hyperplasia	Accuracy
100-2198	14	0	1.00
20-99	4	4	0.50
1-19	2	3	0.40

across split internal jugular vein samples positively correlates with the side of a parathyroid adenoma regardless of preoperative imaging results. Furthermore, the study reinforces that unilateral adenomas exhibit a larger gradient when compared to those of multiglandular disease. Gradients above 100 pg/ml are 100% accurate in predicting a parathyroid adenoma as the root cause of the hyperparathyroidism and the laterality of its location. It is important to note that one-sided minimally-invasive parathyroidectomies can be performed as a same-day outpatient procedure while bilateral four gland explorations require postoperative inpatient monitoring for several days. By better discerning which patients require invasive surgeries, improvements in efficiency, cost reduction and morbidity reduction can be achieved and are worthwhile avenues for future studies. It is unclear if the fidelity of the sestamibi scan has improved over time. In the original study, 41% of the study population had non-localizing sestamibi scans; 29.5% of patients in the newer cohort have non-localizing studies but the difference in these proportions is statistically insignificant ($p=0.24$). 4D CT became available for this institution in 2013. Of the few studies using this technique, one scan correctly reconciled otherwise conflicting locations of an adenoma, two scans correctly identified the location of adenomas where sestamibi scan was inadequate and one scan incorrectly predicted a single mass in the presence of multiglandular disease. Relatively low numbers of 4D CT use limit the ability to make quantitative statements on its accuracy at this time [7]. The PTH gradient also demonstrated utility in reconciling cases where localization studies presented conflicting findings. There were nine documented cases where sestamibi scan, neck ultrasound or 4D CT findings were in disagreement. Of these nine cases, the PTH gradient was correctly predictive of the side in eight of the cases. A ROC curve assesses the statistical validity of a diagnostic test. It is a valuable tool because its output is independent from user selection of arbitrary significance cutoffs [8]. In this context, the ROC curve demonstrates that the PTH gradient is a statistically sound method of differentiating tumor side and etiology. In between the original study and this update, other articles have argued for and against the utility of bilateral internal jugular vein sampling as a means of localizing tumors when preoperative imaging has failed [9-14]. Ito et al. [12] demonstrated that bilateral IJV PTH sampling provided useful positional information when the PTH level of one side was greater than the other by 5%. However, this study did not reconcile the changes in PTH levels seen with multiglandular disease. To date then, this is the only study to demonstrate that a threshold gradient can be used to predict location and the likelihood of adenoma

vs. multiglandular disease. The limitations of our study stem from a relatively small sample size of 115, all of which come from a single tertiary institution. This may result in a more complicated patient base and one that may not be applicable to other populations.

Conclusion

Based on our study, split internal jugular vein IO-PTH gradients serve as a valuable tool when preoperative diagnostic imaging is uncertain. For these patients, PTH gradients exceeding 100 pg/ml were a 100% accurate in predicting the presence of a single adenoma in addition to its location. Below this point, suspicion for multiglandular hyperplasia should be increased and the threshold for a full exploration should be low. Because of its utility, we have used and continue to use this technique at our institution with great benefit.

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