Laterality of central venous sampling: lack of effect on the accuracy of intraoperative parathyroid hormone monitoring

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Abstract

BACKGROUND: The purpose of this study was to determine if laterality of internal jugular vein (IJV) sampling affects the accuracy of intraoperative parathyroid hormone (PTH) monitoring during parathyroidectomy for primary hyperparathyroidism.

METHODS: In this study, 109 patients underwent parathyroidectomy (82 with unilateral disease, 27 with multigland disease). PTH samples were taken from both the left and the right IJV at these time points: preincision (baseline) and then at 5, 10, and, in selected patients, 20 minutes after excision. The Miami criterion was used to determine operative success.

RESULTS: In all 109 patients combined, the mean decreases in intraoperative PTH levels were 73.8 ± 22.2% for the left IJV and 71.9 ± 23.0% for the right IJV (P = .22). The Miami criterion was met in 105 patients: in 100 (95%) left IJV samples and 99 (94%) right IJV samples (P = 1.00).

CONCLUSIONS: No difference was found in the accuracy of intraoperative PTH monitoring between patients’ left and right IJV samples. Central venous laterality did not affect fulfillment of the Miami criterion.

In the United States, primary hyperparathyroidism is the most common cause of hypercalcemia, with an incidence of 36.3 to 120.2 per 100,000 in women and 13.4 to 35.6 in men.1 Up to 85% of cases are caused by a single parathyroid adenoma, facilitating the use of minimally invasive surgery for successful treatment. Despite recent reports that advocate abandoning the minimally invasive approach,2 it is still routinely used by many experienced endocrine surgeons.3 Modern technologic advances—such as 99mTc sestamibi scanning, single-photon emission computed tomography, ultrasonography, and 4-dimensional computed tomography—now enable a degree of disease localization that makes a minimally invasive parathyroidectomy as effective as a conventional bilateral neck exploration.

Intraoperative parathyroid hormone (PTH) monitoring plays a pivotal role in a minimally invasive parathyroidectomy; such monitoring allows rapid intraoperative biochemical evaluation of operative success in patients with primary hyperparathyroidism.4 Given the short half-life (3 to 5 minutes) of PTH, operative success can be confirmed by what is known as the Miami criterion (defined as a > 50% decrease in PTH levels from baseline to 10 minutes after excision), which was first proposed and studied by Irvin et al1 in 1991.
Previously, Abdel-Misih et al. demonstrated that central venous sampling for intraoperative PTH monitoring is an efficacious, acceptable, and anatomically convenient alternative to the more traditional peripheral sampling. In our study, our purpose was to determine, in a group of patients with primary hyperparathyroidism, whether the accuracy of intraoperative PTH monitoring during a parathyroidectomy was affected by left versus right internal jugular vein (IJV) sampling.

Methods

From July 2009 through June 2012, a total of 109 patients with primary hyperparathyroidism enrolled in our prospective study, which was approved by the institutional review board at the University of Arizona. Included were patients with newly diagnosed primary hyperparathyroidism who underwent parathyroidectomy with intraoperative PTH monitoring and then returned for follow-up appointment that included calcium level assessment at 6 months. A total of 79 patients with persistent or recurrent primary hyperparathyroidism, secondary or tertiary hyperparathyroidism, or incomplete follow-up were excluded.

For purposes of preoperative localization, all 109 patients in our study group underwent \(^{99m}\)Tc sestamibi scanning and neck ultrasonography. Patients with negative or discordant results underwent bilateral neck exploration. Patients with concordant results on those 2 imaging studies initially underwent focused parathyroidectomy (ie, a targeted approach to remove the diseased gland without visualization of the other 3 parathyroid glands). However, if an abnormal parathyroid gland was not visualized at the location of interest, or if the intraoperative PTH level did not fall appropriately after resecting a presumed double adenoma.

All 109 patients underwent parathyroidectomy with intraoperative PTH monitoring. We drew PTH samples from both the left and the right IJV at these time points: preincision (baseline) and then at 5, 10, and, in selected patients, 20 minutes after excision. To determine operative success, we used the Miami criterion \(^{5,7}\) (≥50% decrease in PTH from preincision or preexcision values at 10 minutes after excision).

To determine any statistically significant differences in PTH levels (at the various time points) in each of our 109 patients, we used a 2-tailed, matched-pair Student’s \(t\) test. In addition, we conducted separate analyses in patients with single adenomas and in patients with double adenomas on the ipsilateral side who were successfully treated. To assess the frequency of fulfillment of the Miami criterion, we used Fisher’s exact test.

Results

During our 36-month study period, 109 patients underwent parathyroidectomy according to our inclusion criteria: 78 women (mean age, 60.8 years) and 31 men (mean age, 62.5 years). Of the 109 patients, 82 had unilateral disease: 74 (68%) had single adenomas and 8 (7%) had double adenomas. The remaining 27 patients (25%) had bilateral disease with multigland hyperplasia (Table 1).

In 105 patients (96%), the operation was successful. In the 4 patients whose operations failed, the causes were an intrathyroidal adenoma (n = 1) and descended mediastinal adenomas that were not accessible by a cervical approach and thus required a subsequent video-assisted thoracoscopic parathyroidectomy (n = 3). Three patients had nonlocalizing studies. In 1 patient, the preoperative localizing studies suggested a high mediastinal adenoma that appeared resectable from the neck. After failed neck

<table>
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<tr>
<th>Table 1</th>
<th>Characteristics of patients undergoing parathyroidectomy for primary hyperparathyroidism</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Men</td>
<td>31</td>
</tr>
<tr>
<td>Women</td>
<td>78</td>
</tr>
<tr>
<td>All cases</td>
<td>109</td>
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<table>
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<tr>
<th>Miami criterion met</th>
<th>Both sides concordant</th>
<th>Discordant results</th>
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<tbody>
<tr>
<td>All cases</td>
<td>105</td>
<td>94</td>
</tr>
<tr>
<td>Single adenoma</td>
<td>73</td>
<td>65</td>
</tr>
<tr>
<td>Ipsilateral double adenoma</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Bilateral hyperplasia</td>
<td>26</td>
<td>24</td>
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exploration, a delayed video-assisted thoracoscopic parathyroidectomy was performed.

We noted 1 false-negative result: the Miami criterion was not met in a patient with normocalcemic primary hyperparathyroidism who was subsequently found to have restored eucalcemia and a normal PTH level. And we noted 1 false-positive result: the Miami criterion was met in a patient subsequently found to have persistent primary hyperparathyroidism requiring a reoperation for a mediastinal adenoma.

In all 109 patients combined, the mean decreases in intraoperative PTH levels were 73.8 ± 22.2% for the left IJV and 71.9 ± 23.0% for the right IJV (P = .22). In patients with single adenomas, the mean decreases were 76.0 ± 17.6% for the left IJV and 74.1 ± 16.1% for the right IJV (P = .36). In patients with double adenomas on the ipsilateral side who were successfully treated, the mean decreases were 82.9 ± 11.5% for the left IJV and 74.4 ± 18.6% for the right IJV (P = .13). In patients with multigland hyperplasia, the mean decreases were 72.3 ± 16.2% for the left IJV and 72.8 ± 19.3% for the right IJV (P = .83).

The Miami criterion was met in 105 patients: in 100 (95%) left IJV samples and 99 (94%) right IJV samples (P = 1.00). In patients with single adenomas, 70 (96%) had appropriate decreases per the left IJV and 68 (93%) per the right IJV (P = .72). In patients with double adenomas on the ipsilateral side who were successfully treated, 6 (100%) had appropriate decreases per the left IJV and 5 (83%) per the right IJV (P = 1.00). In patients with multigland hyperplasia, 24 (89%) had appropriate decreases per the left IJV and 26 (96%) per the right IJV (P = .61).

We further sought to determine whether laterality affected the accuracy of the Miami criterion in patients with single adenomas and in patients with double adenomas on the ipsilateral side who were successfully treated. In patients with single adenomas, 71 (96%) had appropriate decreases per the ipsilateral IJV and 67 (91%) per the contralateral IJV (P = .33). In patients with double adenomas on the ipsilateral side who were successfully treated, 6 (75%) had appropriate decreases per the ipsilateral IJV and 5 (63%) per the contralateral IJV (P = 1.00). In 8 patients with single adenomas, we found discrepancies using the Miami criterion: in 6 of them, the Miami criterion was met for the ipsilateral IJV but not the contralateral IJV; in the other 2 patients, the Miami criterion was met for the contralateral IJV but not the ipsilateral IJV.

For the 74 patients with single-gland disease, minimally invasive parathyroidectomy was successful in 72 cases. On the ipsilateral side, there were 70 true-positives, when the Miami criterion was met and operative cure was confirmed at follow-up, 1 false-positive, 1 true-negative, and 2 false-negatives. This gives ipsilateral IJV sampling a sensitivity of 97.2%, a specificity of 50%, a positive predictive value of 98.6%, and a negative predictive value of 33.3%. On the contralateral side, there were 67 true-positives and no false-positives. There were 2 true-negatives and 5 false-negatives. Consequently, contralateral IJV sampling had a sensitivity of 93.1%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 28.6%.

Comments

Intraoperative PTH monitoring has been successfully used to guide the extent of an individual patient’s parathyroidectomy. In our study, we found no difference in the decrease in PTH levels, or in the accuracy of the Miami criterion, when using the left versus right IJV for sampling; this finding applied to patients with single adenomas as well as to patients with double adenomas on the ipsilateral side who were successfully treated and those with bilateral disease. Furthermore, we detected no statistically significant change in the accuracy of the Miami criterion between IJV sampling on the ipsilateral and contralateral sides.

Consensus has not yet been reached on the optimal criterion (or criteria) for defining biochemical cure as a measure of operative success in patients with primary hyperparathyroidism who undergo parathyroidectomy. In our study, we used the widely accepted Miami criterion. Richards et al compared the accuracy of the Miami criterion with that of the “Mayo protocol,” which uses the Miami criterion but also requires a postexcision PTH level at 10 minutes that is within the normal range. Adding that 2nd parameter gives the Mayo protocol more specificity (86%) than the Miami criterion alone (68%) while preserving its sensitivity. In our study, we did not specifically compare the Miami criterion and the Mayo protocol.

But in our study, we did look at ipsilateral and contralateral sampling in the context of unilateral disease. Split venous PTH sampling has been proposed as a method of localizing disease when sestamibi scanning fails to do so. Although Alvarado et al did not find bilateral IJV sampling to be a useful tool in directing minimally invasive parathyroidectomy, many other investigators have reached the opposite conclusion. For example, Maceri et al reported an accuracy of 100% in their patients with PTH gradients >200 and 88% in their patients with gradients of 20 to 200.

Because the Miami criterion uses peripheral venous sampling, the magnitude of decreases in PTH levels may differ between sampling sites relative to a single adenoma even as the frequency of fulfillment of the criterion remains the same. Furthermore, Barczynski et al found that in patients whose sestamibi scan results were negative, the addition of bilateral IJV sampling to ultrasonography increased the true-positive rate to 65.4% from 33.3% with ultrasonography alone. Our finding that the accuracy of the Miami criterion does not differ between ipsilateral and contralateral sampling in patients with unilateral disease is particularly useful.

The limitations of our study include its relatively small sample size of 109 (and thus its possible underpowering), its single-center nature (which may limit its external
validity to other populations), and its short follow-up time (6 months postoperatively, with no long-term data available to address any disease recurrence). Moreover, as stated above, our study was not designed to address the accuracy of PTH sampling with normal postexcision levels at 10 minutes (Mayo protocol) but rather focused on the Miami criterion alone.

Conclusions

We found no difference in the accuracy of intraoperative PTH monitoring between our patients’ left and right IJV samples; central venous laterality did not affect fulfillment of the Miami criterion. Furthermore, we found no difference in the accuracy of the Miami criterion for ipsilateral and contralateral sampling in patients with unilateral disease. In our patients with primary hyperparathyroidism, the side selected for central venous sampling (left vs right IJV) during their parathyroidectomy did not affect operative success, but results were useful in accurately predicting operative failure.

Acknowledgment

We would like to thank Mary Knatterud, Ph.D., for editing this report.

References


Discussion

Edward Nelson, M.D. (Salt Lake City, UT): I would like to thank the Southwestern Surgical Congress for the opportunity to discuss this nicely written and very well presented paper. First, an editorial comment: I think this paper is 1 of several that validates the usefulness of intraoperative PTH. Your manuscript talks about the controversy in the literature in the group from Florida, Dr Norman’s group, who had an article in JACS last year entitled “Abandoning Unilateral Parathyroidectomy.” For those of us who haven’t done 15,000 parathyroids, as is part of that title, I think this technique still is probably the gold standard. Your hypothesis is very simple; it is sort of a reverse preop venous sampling. Does it make a difference which side you sample from in terms of the IJV? The answer is equally simple, it doesn’t. There is no difference based on the size of the adenoma, and there is no difference based on whether it was an adenoma or hyperplasia or multiple adenomas. I think your study is a reminder that intraoperative PTH really has 2 goals. The first is to find the disease and have a low rate of recurrence. Although your follow-up was short, I think it is 1 of many studies that proves that it is pretty reasonable. The second is to do a minimally invasive procedure with a low cost and a low morbidity. And I think once again your study validates that as well. I have 3 questions for you: First, your rate of multigland disease is higher than others have reported—about 10% higher. Why is that? And what other preoperative imaging do you use when you suspect multigland disease? In other words, if the ultrasound and the sestamibi scan are confusing or contradictory, what is your next preoperative test, if any? Second, I assume you still do frozen sections. If you do, did you see any correlation specifically in the patients who you had a missed adenoma. And finally, there is a literature on intraoperative PTH and secondary hyperparathyroidism. I am wondering whether your institution is using it. And even the next step, are you using it when you have a patient who has had a total parathyroidectomy and now has recurrent disease from implants in their arm.

Once again I think you did a very nice job presenting. It was a pleasure to read the manuscript.

Mr Lev N. Korovin, B.S. (Tucson, AZ): Thank you very much for the questions. To answer the first one, there is more multigland disease in our study which I would attribute to referral bias. We are a tertiary referral center which gets patients from all over Southern Arizona, and we do get a disproportionately higher number of both patients with
multigland disease and ones who fail localization with sestamibi scan. In terms of the imaging that we use, we do our own ultrasound for all referred patients. If localization is still not achieved with the sestamibi and ultrasound, then no additional imaging gets done; however, with this particular study, all patients had bilateral internal jugular venous sampling; so effectively, we were doing split venous sampling which can also be used for lateralization. However, these patients were still more likely to have bilateral neck exploration. Secondly, frozen sections are routinely done at our institution. In terms of the 4 operative failures, which 3 of them were descended mediastinal adenomas and 1 of them was a small intrathyroidal adenoma, there is a correlation, specifically in terms of cellularity. Cellularity was either normal or borderline, around 50%. For the third question, using intraoperative parathyroid hormone for secondary parathyroidism as opposed to total parathyroidectomy with implant, the study looked only at primary hyperthyroidism; and being a medical student, I have difficulty speaking for what is typically done at our institution. However, it certainly is reasonable to perform intraoperative hormone monitoring for both of these situations because even though frozen section will tell you if you removed parathyroid tissue and whether or not it was hypercellular, ioPTH is still the only method of intraoperatively determining biochemical cure. Thank you once again for your questions.