Annals of Medicine and Surgery 6 (2016) 64–67

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.annalsjournal.com

Focused parathyroidectomy without intra-operative parathormone monitoring: The value of PTH assay in preoperative ultrasound guided fine needle aspiration washout

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HIGHLIGHTS

- Preoperative FNA-PTH washout and intraoperative US together give accurate information about localization of parathyroid adenomas.
- In this circumstances, focused parathyroidectomy without intraoperative PTH monitoring might be feasible and successful.
- Nevertheless, misdiagnosis due to concomitant nodular thyroid disease is a fact that always merit consideration.

ARTICLE INFO

Article history:
Received 11 October 2015
Received in revised form
16 November 2015
Accepted 11 December 2015

Keywords:
Parathyroid
Washout
Parathyroidectomy

ABSTRACT

Background: The accurate identification of hyperfunctioning parathyroid (HP) gland is the only issue for definitive surgical treatment in primary hyperparathyroidism (pHPT). Various imaging and operative techniques have been proposed to confirm the localization of the diseased gland. Nevertheless, none of these methods proved to be the gold standard. The presented study aimed to assess the value of parathyroid hormone assay in preoperative ultrasound guided fine needle aspiration (FNA)-PTH washout fluid to verify the correct localisation for focused parathyroidectomy without intra-operative PTH monitoring.

Material and Methods: The retrospective analysis of 57 patients with pHPT who underwent FNA-PTH was conducted from a prospective database. Biochemical assessment together with radiological (ultrasonography) and nuclear (MIBI scan) imaging was reviewed. Associations between FNA-PTH washout values and localization technics were evaluated and compared in terms of operative findings.

Results: Focused parathyroidectomy without intraoperative PTH monitoring was performed to 45 patients with high FNA-PTH values. The median largest diameter of the target parathyroid lesion identified by ultrasonography was 13 mm (range, 6 to 36). The median serum PTH level was 190 pg/mL (range, 78 to 1709; reference range, 15 to 65) whereas the median washout PTH was 2500 pg/mL (range, 480 to 3389). According to operative findings high FNA-PTH levels correctly identified parathyroid adenoma in 40 cases (89% of sensitivity and 100% of specificity and positive predictive value) whereas MIBI scan localized the lesion in 36 of these cases (80% of sensitivity).

Conclusions: The higher level of PTH in preoperative ultrasound guided FNA washout is a considerable data to predict the correct localization of HP, particularly in circumstances of greater values than the serum PTH level. However, although its specificity is high, in cases of coexisting nodular thyroid disease, associated additional HP might be missed at focused parathyroidectomy without PTH monitoring, leading to recurrent disease.

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http://dx.doi.org/10.1016/j.amsu.2015.12.065

1. Introduction

Primary hyperparathyroidism (pHPT) is an endocrine disorder mainly caused by solitary or multiple hyperfunctioning parathyroid (HP) lesions (hyperplasia, adenomas, or rarely carcinomas) [1,2]. The accurate identification of diseased gland is the major issue for definitive surgical treatment [3]. Conventionally, bilateral neck exploration with intraoperative PTH monitoring has been standardized to achieve the goal of higher surgical success. Nevertheless, there exists some controversies particularly in cases of concomitant nodular thyroid disease [4]. Intraoperative identification of the pathology is not always possible, even in the hands of the most experienced surgeons. Therefore, preoperative localization is a crucial issue with debate currently [5]. Preoperative accurate localization of diseased gland has the potential to reduce surgical time, decrease complication rates, prevent technical failures together with the necessity of secondary interventions, and make minimally invasive parathyroidectomy possible as the preferred option for surgical treatment [6,7]. Neck ultrasound and dual-phase technetium-99m-sestamibi scan are the most commonly used tools in the diagnostic approach of pHPT [8]. MIBI scan has ability to localize HP in pHPT patients with high sensitivity (71–93%) and spesificity (90%) [9]. Neck ultrasound is the least invasive and cost-effective method [10,11] to accurately localize HP, but its efficacy is related to the operator experience and may be reduced in the presence of concomitant nodular goiter [12,13]. There have been interest and controversy regarding the utility and safety of ultrasound-guided parathyroid FNA. First described by Doppman et al. [14] in 1983, parathyroid FNA with PTH washout became more frequently used during the late 1990s and thereafter, when several institutions reported their experience [15–21]. Our objectives were to analyze our institutional experience with parathyroid FNA for performing PTH washout and to report its performance statistics, safety, and limitations to route focused parathyroidectomy.

2. Materials and methods

2.1. Patients

A retrospective analysis of 57 consecutive patients who underwent focused parathyroidectomy with preoperative ultrasound guided parathyroid FNA and washout at a tertiary reference center between 2010 and 2015 were conducted. The medical records were reviewed for clinical presentation, biochemical measurements, cervical ultrasonography, parathyroid sestamibi scan, parathyroid FNA procedure, surgical treatment, pathology reports, and procedure-related complications.

2.2. Patient characteristics

All patients were admitted with initial presentation of pHPT. Demographic data, pertinent clinical information (bone disease, kidney stones, or any subjective symptoms related to hyperparathyroidism), neck surgical history (number of parathyroid or thyroid explorations), and history of radiation therapy were gathered.

2.3. Biochemical data and imaging

Preoperative serum PTH, calcium, phosphorus, albumin, 25-OH vitamin D and 24-h urine calcium levels were analyzed.

Cervical ultrasonography reports were reviewed for the diameter and the localization of the suspected parathyroid lesion, and the presence of multinodular goiter, if present. Localization details were also recorded from the parathyroid sestamibi scans, including the description of multifocality of a lesion.

2.4. Technique for parathyroid FNA and PTH washout

FNA of the parathyroid gland was performed under continuous, real-time, ultrasound visualization with use of a 7.5-MHz linear transducer (GE Logiq 5, California, USA). Before the FNA, the skin was cleansed with a povidone-iodine solution. Sterile gel was used as a coupling agent. A 22-gauge standard, noncutting, bevel-edge needle was inserted by using a freehand technique. The needle was moved several times in a back-and-forth motion within the mass (just for parathyroid glands that appear hyperplastic on ultrasound), and material from the target lesion was obtained through capillary action, without the use of attached suction. For the washout procedure, isotonic saline was drawn into the needle to fill the needle hub, after which it was then expelled through the needle into a plastic tube. A total of 1 mL of blood-tinged fluid was submitted for PTH assay. At our institution, no established reference ranges for PTH in needle wash specimens currently exist.

2.5. Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 16.0). Continuous variables are expressed as means ± standard deviation or medians (ranges) on the basis of distribution of the data. Univariate logistic regression analysis was used to identify variables associated with positive parathyroid FNA results. Variables having a statistically meaningful effect were included in multivariate regression analysis. Significance was established at $P < .05$.

3. Results

Between 2010 and 2015, 41 female and 16 male patients underwent a total of 57 ultrasound-guided parathyroid FNA procedures with the diagnosis of pHPT. The mean age was 56.09 ± 12.43 years. The most common signs and symptoms at presentation were fatigue, bone pain and urolithiasis, however, 8 patients were admitted because of incidental hypercalcemia for further workup.

The preoperative median serum PTH level was 190 pg/mL (range, 78 to 1709). The mean serum levels of calcium, phosphorus and 25-OH Vitamin D were as follows; 11.5 mg/dL (range, 10.4 to 13.7), 2.69 mg/dL (range, 1.4 to 3.8) and 19.28 ng/mL (range 5.6–43.1), respectively. The mean urine calcium was found to be 348.37 mg/day. The demographic and biochemical features of the patients are shown in Table 1. The median largest diameter of the target parathyroid adenomas in 57 patients identified by ultrasonography was 13 mm (range, 6 to 36). Ultrasonographic evaluation revealed multinodular goiter in 22 (38%) and nodular goiter in 7 patients (12%). Parathyroid sestamibi scanning (MIBI) detected suspicious parathyroid lesions in 47 (%82.4) of 57 patients. In 10 patients with negative MIBI results, ultrasonographic imaging demonstrated 7 lesions on the right and 3 on the contralateral side that is verified by positive PTH washout. Seven out of ten patients with negative MIBI results (%63.6) found to have nodular thyroid disease. Moreover, in two cases with discordant MIBI and US results, US guided PTH washout proved accurate localization.

In 51 of 57 patients (89%), FNA-PTH values were high enough to be detected. Higher PTH levels than serum was considered as positive according to the literature. FNA-PTH values were above serum PTH levels in 47 (82%) of 57 patients. The median washout PTH value was 2500 pg/mL (range, 480–3389). Focused parathyroidectomy was performed to 45 patients (78%) by means of intraoperative sonographic guidance; the rest 12 patients were lost to follow-up. Accordingly the sensitivity of MIBI was found to be

Table 1
Demographic and biochemical features of the patients.

Feature	Patient (n = 57)
Gender (Female/Male)	41/16
Mean age	56.09 ± 12.43
Mean PTH level (15–65 pg/mL)	282 ± 316.79 (78–1709)
Mean calcium (8.8–10.6 mg/dL)	11.5 ± 0.73 (10.4–13.7)
Mean urine calcium (100–300 mg/day)	348.37 ± 220.20
Mean phophorous (2.4–5.1 mg/dL)	2.69 ± 0.54 (1.4–3.8)
Mean 25-OH vitamin D (20–30 ng/mL)	19.28 ± 8.58 (5.6–43.1)
Renal stone (n,%)	12 (21%)
Osteoporosis/Osteopenia	20/31
Mean size of paratiroid adenomas	13 mm (6–36)
Mean level of PTH washout pg/mL (n = 47)	2007.08 ± 12.13 (480–3389)
Histopathology (n = 45) (adenoma/hyperplasia/carcinomas	37/4/4
Single adenoma/Multiple adenomas	37/4

80% in our series. Intraoperative sonographic examination confirmed that high FNA-PTH values correctly identified HP in 40 cases, with a sensitivity of 89%. Intraoperative PTH monitoring was not performed. Frozen section analysis of the resected specimens verified the diagnosis in every case. Histopathologic evaluation revealed single parathyroid adenoma in 37 patients (82%), parathyroid carcinoma in 4 patients (9%), and parathyroid hyperplasia and double parathyroid adenoma in 4 patients (9%).

4. Discussion

Bilateral neck exploration of all four pararthyroid glands has traditionally been the standard surgical approach for the treatment of pHPT. However, there are risks of hypoparathyroidism in the immediate postoperative period and recurrent laryngeal nerve injury. This issue has been examined by numerous reports with evidence that targeted surgeries based on preoperative accurate localization. Focused surgical interventions achieve similar cure rates with a lower risk of complications, shorter operating times and hospital stays with significant cost-savings and better cosmetic results in patients with solitary parathyroid adenomas [22,23]. In our study, no complications related to fine needle aspirations were existed to report. The major question at this point is to identify the best method to predict the accurate localization. US and sestamibi scan are two of the most common modalities for this purpose. US permits anatomical detection of an enlarged parathyroid gland and accurate localization relative to the thyroid gland, although the presence of co-existing nodular thyroid disease reduces the specificity and sensitivity [24]. There are a variety of scintigraphic methods that can be used in the evaluation of pHPT. The combination of these methods has been shown to increase the overall sensitivity for localization of solitary parathyroid adenomas, up to 95% [25–28]. Nevertheless, this might be either insufficient or discordant in some cases. This study demonstrates a clear discrepancy between US and scintigraphy in approximately 20% of cases with comcomitant nodular thyroid disease. Surgeons should also be aware that both US and scintigraphy might be unable to differentiate a low superior parathyroid adenoma from an inferior parathyroid adenoma, which remains a potential source of error.

In the last few decades intraoperative PTH assay has become an important adjunct for definitive surgical treatment. However, many centers, like ours, do not have the opportunity to perform intraoperative PTH assay. Therefore, preoperative US guided FNA and PTH washout became the method of choice for the suspicious lesions in patients with symptomatology indicating parathyroid lesions on neck ultrasound. Parathyroid FNA with PTH washout provides a more certain localization of the suspicious parathyroid lesion in the preoperative setting. In the hands of various operators and a setting of heterogeneous groups of patients, US-guided parathyroid FNA with PTH washout was reported to have a specificity of 91%–100% and a sensitivity of 91%–100% [15,16,18]. Barczynski et al. [16] concluded that a PTH assay in US-guided FNAs of suspicious parathyroid lesions may be used to establish the nature of the mass, distinguish the parathyroid and nonparathyroid tissues (goitre, lymph nodes) and improve the accuracy of US parathyroid imaging, allowing for successful directing of surgical approach in a majority of patients. In our series, positive washout results predicted the accurate localization in all, except five patients with concomitant nodular thyroid disease, with a sensitivity of 89%. Our data demonstrated that a level of PTH washout above the serum PTH level is a valid indication that HP was sampled. Because a cutoff value is needed, any value in the parathyroid tissue sample higher than the serum PTH was considered as cutoff point. However, further studies with larger number of cases at different institutions are needed to determine the FNA-PTH cutoff value that is required to confirm the HP.

Intraoperative US guided focused parathyroidectomy has been successfully performed in all patients. In 36 of these cases, the localization of the parathyroid adenoma was in accordance with MIBI scan. The diagnostic accuracy of sestamibi scan in this series was 80%, whereas intraoperative sonography was found to be superior with a sensitivity of 100%. This discordance might be attributed to the higher rate of concomitant nodular thyroid disease (63%) misleading sestamibi scanning at our endemic region.

Intraoperative US guided focused parathyroidectomy has been successful in all 45 patients. However, PTH washout correctly predicted the accurate location in 40 but 5 patients with coexisting nodular thyroid disease. This study highlights the relative merits of combination of intraoperative US guidance with PTH washout for localizing solitary parathyroid adenomas with greater sensitivity and accuracy in the presented patient cohort. Surgical intervention was curative in all 45 patients (100%), nevertheless 2 patients (4%) with concomitant thyroid disease developed recurrent hyperparathyroidism 3–6 months after surgery. This issue deserves more consideration when planning focused parathyroidectomy without PTH monitoring, particularly in endemic regions for thyroid disease.

The results of this study clearly show that higher PTH washout value of FNA in association with intraoperative US guidance is as highly accurate, sound and successful way in determining the location of the parathyroid pathology and performing definitive surgical therapy without intraoperative PTH monitoring in pHPT. However, although its specificity is high, in cases of coexisting nodular thyroid disease, associated additional HP might be missed preoperatively, leading to recurrent disease after focused parathyroidectomy without PTH monitoring.

5. Conclusion

In conclusion the combined use of preoperative FNA-PTH washout and intraoperative US guidance is advocated for the accurate localization of parathyroid adenoma in patients with pHPT. In this circumstances, focused parathyroidectomy without intraoperative PTH monitoring might be feasible and successful. Nevertheless, misdiagnosis due to concomitant nodular thyroid disease is a fact that always merit consideration.

Conflicts of interest

None.

Ethical approval

Ethical Approval was given by Local Ethics Committee of Bulent Ecevit University Faculty of Medicine. The reference number is 2345/2015.

Funding

None.

Author contribution

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Writing: Dilek Arpaci.
Nuclear Imaging: Tarik Elri.
Burak Bahadir: Pathology review.

Consent

Informed consent from patients was taken.

Guarantor

Dilek Arpaci.

Acknowledgment

Authors declared that no conflict of interest.

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