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The diagnostic value of parathormone washout in Tc-99m MIBI negative primary hyperparathyroidism cases

Tc-99m MIBI Negatif Primer Hiperparatiroidizm Olgularında Parathormon Yıkamanın Tanısal Değeri

Hakan Korkmaz[1*]

1Suleyman Demirel University, Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology, Isparta, Turkey

ABSTRACT

Aim: To determine the sensitivity and positive predictive value (PPV) of the measurement of parathormone (PTH) in fine needle aspiration (FNA) washout fluid, in the preoperative localization of hyperfunctional parathyroid lesions.
Methods: Medical records of patients diagnosed with primary hyperparathyroidism (PHPT) in our clinic between 2016-2020 were retrospectively evaluated. Thirty-six patients with PHPT who underwent preoperative FNA-PTH washout procedure were included in the study. FNA-PTH washout was only performed in patients with negative technetium-99m methoxy isobutyl isonitrile / single photon emission computed tomography (Tc-99m MIBI/SPECT) imaging. It was accepted to be higher than plasma PTH level as positive cut-off value for PTH washout in determining parathyroid lesions. Sensitivity, PPV, false positive, false negative and diagnostic accuracy values of PTH washout were calculated.
Results: PTH washout was false positive in 2 cases, false negative in 1 case and true positive in 33 cases. In the discrimination of true parathyroid lesions, the sensitivity of PTH washout was calculated as 97.05%, PPV 94.29% and diagnostic accuracy 91.67%. PTH washout levels correlated positively with plasma PTH and parathyroid lesion volüme (respectively, r=0.347, p=0.041 ve r=0.356, p=0.036). All patients tolerated the FNA-PTH flushing procedure well and no complications developed afterwards.
Conclusion: The FNA-PTH washout is a safe and useful method to localise parathyroid lesions in PHPT patients with negative Tc-99m MIBI/SPECT imaging.

Key words: Fine needle aspiration, MIBI/SPECT negative, primary hyperparathyroidism, washout

ÖZ

Amaç: Hiperfonksiyon gösteren paratiroid lezyonlarının preoperatif lokalizasyonun-da ince iğne aspirasyonu (İİA) yıkama sıvısında parathormon (PTH) ölçümünün du-yarlılık ve pozitif prediktif değer (PPD)'ini belirlemek.
Yöntem: 2016-2020 yılları arasında kliniğimizde primer hiperparatiroidi (PHPT) tanısı alan hastaların tıbbi kayıtları retrospektif olarak inceledik. Operasyon öncesi İİA-PTH yıkama prosedürü uygulanan 36 PHPT hastası çalışmaya alındı. İİA-PTH yıkama, sadece teknesyum-99m metoksi-isobutil-isonitril / tek foton emisyonlu bilgisayarlı to-mografi (Tc-99m MIBI/SPECT) negatif hastalarda yapıldı. Serum PTH seviyesinden daha yüksek PTH yıkama seviyeleri, pozitif kesme değeri olarak tanımlandı. İİA-PTH yıkama prosedürünün duyarlılık, PPD, yanlış pozitif, yanlış negatif ve tanısal doğruluk değerleri hesaplandı.
Bulgular: PTH yıkama 2 olguda yanlış pozitif, 1 olguda yanlış negatif ve 33 olguda gerçek pozitifti. Gerçek paratiroid lezyonların ayırt edilmesinde PTH yıkamanın du-yarlılığı %97.05, pozitif prediktif değeri %94.29 ve tanısal doğruluğu %91.67 olarak hesaplandı. PTH yıkanma seviyeleri, serum PTH ve paratiroid lezyon hacmi ile pozitif koreleydi (sırasıyla, r=0.347, p=0.041 ve r=0.356, p=0.036). Tüm hastalar İİA-PTH yıkama işlemini iyi tolere etti ve sonrasında herhangi bir komplikasyon gelişmedi.
Sonuç: İİA-PTH yıkaması, Tc-99m MIBI/SPECT negatif PHPT hastalarında paratiroid lezyonlarını lokalize etmek için güvenli ve kullanışlı bir yöntemdir.

Anahtar sözcükler: İnce iğne aspirasyonu; MIBI/SPECT negatif; primer hiperparatiroidizm; yıkama

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*Corresponding Author: Hakan Korkmaz. Suleyman Demirel University, Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology, Çünür, Isparta/Türkiye. +905059303322, drhkorkmaz@yahoo.com.tr

ORCİD: 0000-0001-5066-6335

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disease characterized by hypercalcemia as a result of excessive parathormone (PTH) secretion of one or more parathyroid glands [1]. Although the traditional treatment of PHPT is bilateral neck exploration surgery, minimally invasive parathyroidectomy (MIP) has become the preferred method thanks to the development of tabpreoperative imaging methods. MIP has advantages, such as shorter operation time and hospital stay, smaller incision requirement, faster recovery and less pain. The selection of patients suitable for MIP and the success of surgery depend on the precise localization of the preoperative hyperfunctional parathyroid lesion [2, 3].

The most common imaging methods for the detection of hyperfunctional parathyroid lesions are parathyroid ultrasonography (US) and technetium-99m methoxy isobutyl isonitrile (Tc-99m MIBI) parathyroid scintigraphy [4, 5]. When Tc-99m MIBI is used together with single photon emission computed tomography (SPECT), its sensitivity in determining parathyroid lesion increases [6]. In a meta-analysis, the sensitivity and positive predictive value (PPV) of Tc-99m MIBI/SPECT imaging were 78.9% and 90.7%, respectively [6]. In PHPT cases that cannot be localized with parathyroid US and scintigraphic imaging, images such as SPECT / computerized tomography (CT), cervical magnetic resonance imaging and 18F-fluorocholine positron emission tomography (PET)/CT can also be used [8]. However, even when all imaging methods are performed, there are still patients whose parathyroid adenoma cannot be localized.

In PHPT cases with negative Tc-99m MIBI imaging, PTH measurement in the washout fluid of fine needle aspiration (FNA) of suspicious lesions identified by the US is an important procedure [9]. Although there are different recommendations for the positive cut-off value of the PTH wash, no consensus has yet been reached.

In this study, we aimed to present, together with our clinical experience, the cut-off value of FNA-PTH washout after US-guided FNA of suspected lesions identified by parathyroid US in PHPT cases with negative Tc-99m MIBI/SPECT imaging.

MATERIAL AND METHOD

The current study was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. All participants were informed and provided written informed consent.

Selection of Samples

The medical files of patients who were diagnosed with PHPT in our clinic and then underwent parathyroidectomy between 2016 and 2020, were scanned retrospectively. Thirty-six patients in whom in was not possible to detect a parathyroid lesion with Tc-99m MIBI/SPECT imaging and could undergo the US-guided FNA-PTH procedure, were included in the study [mean age 54.47±2.49 years, 27 females (75%), 9 males (25%)]. Demographic features, preoperative laboratory parameters (serum corrected calcium (cCa), phosphorus, magnesium, creatinine, albumin, PTH, 25-hydroxy vitamin D, 24-hour urine calcium excretion), clinical findings related to PHPT (osteoporosis, urolithiasis) and characteristics of suspicious lesions detected by preoperative US, were all recorded. Total serum calcium levels were corrected according to serum albumin levels [10].

The diagnosis of PHPT was made based on the presence of normal or high plasma PTH levels in case of hypercalcemia [1]. Parathyroid US and scintigraphy imaging were performed to determine preoperative localization.

Parathyroid US was performed with a high-resolution device with a 6-13 MHz linear transducer (Philips EPIQ 5, DEU). FNA-PTH washout was only performed in patients with negative Tc-99m MIBI/SPECT imaging.The volume of parathyroid adenoma was calculated by the ellipsoid model formula (length x thickness x width x 0.52)

FNA-PTH Washout Procedure

Neck skin was cleaned with 10% povidone iodine. After entering the suspicious lesion using a sterile 25 gauge needle and 10 mL syringe under US guidance, negative pressure was applied several times with a back-and-forth motion. After the aspirate material came to the injector, it was washed with 1 ml of 0.9% normal saline. Tubes were centrifuged and PTH was analyzed in

supernatant liquid.

PTH levels of both plasma and FNA washout fluid were measured by electro-chemiluminescence immunoassay (Elecsys PTH, Roche Diagnostics, Mannheim, Germany). It was determined that PTH washout was higher than plasma PTH level as a positive cut-off value in identifying parathyroid lesion. All patients with PHPT were operated with the minimally invasive parathyroidectomy method. Histopathological findings were evaluated in surgical specimens.

Biochemical analysis

Serum calcium, phosphorus, magnesium, alanine aminotransaminase (ALT), creatinine, albumin and urine calcium concentrations were measured using a Beckman Coulter AU 5800 chemistry analyzer (Beckman Coulter, Brea, CA, USA). The corrected calcium (cCa) was calculated using the following equation: cCa = [(4 - albumin) × 0.8] + Ca.

Serum 25-hydroxyvitamin D [25(OH)D] was measured by electro-chemiluminescence immunoassay (Elecsys Vitamin D; Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

All statistical analysis were done using the SPSS 22.0. The Shapiro-Wilk test was performed to evaluate the distributions of variables. The data was given as mean ± standard deviation for the variables with normal distribution and was given as the median±interquartile range for those who did not have normal distribution. The sensitivity, PPV, negative predictive value (NPV) and accuracy of PTH washout in determining parathyroid lesions were calculated. True positive, false positive and false negative results of PTH washout were determined based on postoperative histology reports. Correlations between variables were evaluated with the Spearman and Pearson correlation tests. A result of $p < 0.05$ was determined to be statistically significant.

RESULTS

Demographic, clinical and preoperative laboratory features of the groups are given in Table 1. Twelve of the patients with PHPT (33.3%) had osteoporosis and 10 (27.8%) had urolithiasis.

Preoperative PTH washout levels and clinical characteristics of patients with PHPT are given in Table 2. After histopathological evaluation of the parathyroidectomy samples, parathyroid hyperplasia was found in 7 patients (19.4%), parathyroid carcinoma in 1 (2.8%), and parathyroid adenoma in 28 (77.8%). There was no significant difference in terms of PTH washout, plasma PTH and volume of parathyroid lesion between patients with parathyroid adenoma and parathyroid hyperplasia.

Table 1. Preoperative demographic and laboratory characteristics of patients with primary hyperparathyroidism

	Results
Age (years)*	54.47±12.49
Gender (female/male)	27/9
Plasma PTH (ng/L)	139±105
25(OH)D3 (ng/mL)	17.25±14.75
Creatinine (mg/dL)	0.85±0.3
ALT (U/L)	21±6
cCa (mg/dL)	11.16±0.81
Phosphorus (mg/dL)*	2.60±0.49
Magnesium (mg/dL)	2±0.28
Albumin (g/dL)*	4.28±0.41
Urine calcium excretion (mg/day)*	301.51±153.105

Datas expressed as median (±IQR) and *mean (±SD). Parathormone, PTH; 25-hydroxy vitamin D3, 25(OH)D3; alanine aminotransaminase, ALT; corrected calcium, cCa

Table 2. Preoperative PTH washout and clinical characteristics of patients with primary hyperparathyroidism

	Results
PTH washout (ng/L)	4750±15245
Volume of adenoma (cm3)	1.83±0.58
Urolithiasis (n, %)	10 (%27.8)
Osteoporosis (n, %)	12 (%33.3)

Datas expressed as median (±IQR)

PTH washout was false positive in 2 cases, false negative in 1 case and true positive in 33 cases. The sensitivity of PTH washout in determining true parathyroid lesions was 97.05%, PPV 94.29% and diagnostic accuracy 91.67%. No complications developed in any patient after the FNA-PTH washout procedure.

There was a positive correlation between plasma PTH and PTH washout levels ($r=0.347$, $p=0.041$). In addition, there was a positive correlation

between parathyroid lesion volume with plasma PTH and PTH washout levels (r=0.601, p=0.001 and r=0.356, p=0.036, respectively).

DISCUSSION

To our knowledge, this was the largest case study evaluating the diagnostic benefit of PTH washout in PHPT cases with negative Tc-99m MIBI/SPECT imaging. We support the fact that FNA-PTH washout is a safe and useful method for detect whether there is a hyperfunctional parathyroid lesion of suspicious lesions detected by parathyroid US.

Location of the parathyroid lesion is the most important factor affecting surgical success in primary hyperparathyroidism [11]. The most widely used first-line imaging technique for the localization is Tc-99m MIBI. However, there is false negativity in approximately 25% of cases [12]. In a previous study, we found the sensitivity to be 90.4% and the PPV to be 90.2% when we used the parathyroid US and scintigraphy images together [13]. It has been suggested that false negative parathyroid scintigraphy imaging may be related to the histological features and the small size of the lesions [14]. In addition, it has been suggested that parathyroid scintigraphy images can be more useful, especially in cases with hyperparathyroidism with higher serum PTH and calcium levels [15, 16]. In this study, PTH levels of the patients were moderately elevated (139±105 ng/L). In PHPT cases with negative Tc-99m MIBI imaging, FNA-PTH washout is a valuable procedure in determining whether suspicious images detected by US belong to a hyperfunctional parathyroid lesion. With the help of this method, parathyroid lesions can be distinguished from lymphoid and thyroid-derived lesions [9].

There are studies suggesting different positive cut-off values for PTH washout. Gokcay et al. found sensitivity at 90.3% and specificity at 88.9% in determining parathyroid lesion when they received 436.5 pg/mL as the positive cut-off value for PTH washout [17]. Kiblud et al. showed that a PTH washout result of more than 1 000 pg/mL had sensitivity of 75% and PPV of 74% in the verification of parathyroid tissue [18]. When aspiration materials of non-parathyroid lesions are diluted with saline, PTH washout levels are expected to be lower than plasma PTH [19]. There are some studies supporting this idea: in the studies where PTH washout/plasma PTH ratio was accepted as positive cut off above 1, they detected 100% of PPV and specificity of PTH washout [20-23]. In the current study, we also accepted PTH washout/plasma PTH ratio to be above 1 as a positive cut-off value, and we determined the sensitivity of PTH washout to be 97.05%, and PPV to be 94.29%. Gokçay et al. found that the PTH washout/plasma PTH ratio over 3.05 had a specificity of 89% [17]. This data suggests that when higher PTH washout / plasma PTH ratio is accepted as positive cut-off value, it may increase false negative results.

Studies have a shown positive correlations between parathyroid lesion volumes and PTH washout levels [20, 21]. In accordance with the literature, we also found a positive correlation between parathyroid lesion volume and the PTH washout level (r=0.356, p=0.036). Since the PTH washout level correlates between parathyroid lesion size, accepting a fixed number as a positive cut-off value for PTH washout may result in an increase in false negative or false positive results.

More than 90% of PHPT cases are due to parathyroid adenoma, while 6% are due to parathyroid hyperplasia. In this study, 19.4% of PHPT cases were parathyroid hyperplasia. The reason why these are higher than the literature data, may be related to the fact that FNA-PTH washout was only performed in patients with negative Tc-99m MIBI/SPECT imaging. Xue et al. showed that patients with parathyroid hyperplasia have a higher negative Tc-99m MIBI imaging rate [24].

There are some factors limiting the application of FNA-PTH washout. Firstly, it is necessary to identify a potential parathyroid lesion by parathyroid US. Secondly, sufficient aspiration should be performed with a fine needle from the determined lesion: insufficient sampling can cause false negative results. The volume of Tc-99m MIBI negative parathyroid lesions is usually small [25]. In accordance with the literature, parathyroid lesion volume was indeed found to be very low in the current study. In 50% of our cases, the largest size of the parathyroid lesion was less

than 1 cm. In addition, it should be noted that when the lesion is too deep, it may be difficult to reach it with a needle. In this study, only one patient had PTH washout level lower than plasma PTH level. Complications such as bleeding, hematoma, pain and hoarseness may develop as a result of the FNA procedure [9, 25]. However, our cases tolerated the procedure well and no complications developed after the procedure.

Limitations :Our study has some limitations. It is primarily a retrospective study. In addition, we could not comment on the specificity of the procedure, since patients with PTH washout levels lower than plasma PTH (except 1 patient) were not procedured. Studies involving a larger number of patients on which PTH washout negative cases are performed could better demonstrate the effectiveness of this procedure.

Conclusıon: US-guided FNA-PTH washout is an important method in detecting hyperfunctional parathyroid lesions with negative Tc-99m MIBI/SPECT imaging. We suggest that PTH washout is higher than plasma PTH as the positive cut off value during this procedure. However, further studies with a greater number of cases in different institutions are needed to confirm the positive cut-off value of PTH washout.

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Author / ORCID	Authorship Contrubition
Hakan Korkmaz 0000-0001-5066-6335	The author fully involved to all stage of this study and final approved this article.