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Comparison of Methoxyisobutylisonitrile Scintigraphy and Ultrasonography in Preoperative Localization of Secondary Hyperparathyroidism

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Abstract

Background: In patients with secondary hyperparathyroidism, the four glands are not uniformly enlarged; therefore, preoperative localization is difficult in comparison with primary hyperparathyroidism. The aim of this study was to compare the usefulness of 99mTc-sestamibi scintigraphy versus ultrasonography in the preoperative assessment of patients with secondary hyperparathyroidism.

Methods: Between October 2008 and March 2012, 25 uremic patients with secondary hyperparathyroidism underwent 99mTc-sestamibi scintigraphy and high resolution ultrasonography before total or subtotal parathyroidectomy. We measured plasma concentration of intact parathyroid hormone (PTH), calcium, phosphorus, and alkaline phosphatase (ALP) before parathyroidectomy.

Results: Sensitivity and positive predictive value (PPV), respectively, were 47.3% and 97.8% for MIBI scintigraphy, and 69.5% and 96.9% for ultrasonography. The sensitivity of combined techniques was 84.2%. There was a positive correlation between the parathyroid glands' weight and serum calcium level, and positive MIBI scintigraphy and ultrasonography results. However, there was no correlation between the preoperative serum PTH, phosphorus, alkaline phosphatase (ALP), dialysis duration, and parathyroid glands' weight.

Conclusions: Ultrasonography is a reliable non-invasive localization tool. It has greater sensitivity in localizing parathyroid glands in secondary hyperparathyroidism than scintigraphy.

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Introduction

Hyperparathyriodism (HPT) is a situation in which the parathyroid hormone (PTH) is produced in increased levels and results in high serum calcium (Ca) level. HPT is classified into primary, secondary, and tertiary types, based on its underlying cause.

HPT is called primary when the levels of Ca cannot produce a negative feedback on PTH secretion and result in high PTH production from the parathyroid glands. In secondary HPT, high PTH level is a result of the feedback of chronically low calcium levels due to chronic renal failure or malabsorption. In tertiary HPT the triggered parathyroid cells autonomously secrete PTH irrespective to Ca levels and can result in chronic hypercalcemia even after successful renal grafting (1).

Despite the opinion of a number of researchers that there is no need for the glands to be localized, there is evidence that shows a 10%-30% recurrence and failure in total resection of pathologic parathyroid glands during surgery, which indicate the importance of parathyroid localization prior to surgery. It is notable that the experience of the surgeon and localization of the glands are the two most important parameters in a successful surgery. Till recently, exploration in the surgery field was the most used technique to localize the glands; however, in the era of minimally invasive techniques, the pre-surgery localization is more important than ever. This can decrease the surgery period and the side effects, and can presumably lower

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the morbidity rate of the disease (2-7).

There are different modalities which can be used to localize the glands, such as CT scan, MRI, Nucleic Imaging, and angiography. Ultrasound, however, is less invasive and more cost-effective than other methods, but its sensitivity is based on the operator's precision. For example, the parathyroid gland can be easily mistaken with a thyroid nodule or a cyst (8-10) One of the newest methods introduced is technetium scan. Technetium (99mTc) sestamibi (under the trade name of Cardiolite) is a pharmaceutical agent used in nuclear medicine imaging. The drug is a coordination complex of the radioisotope technetium-99m with the ligand methoxyisobutylisonitrile (MIBI). The generic drug became available late September 2008. A scan of a patient using MIBI is commonly known as a "MIBI scan" (11-12). It has been shown that parathyroid gland takes up 99mTc MIBI following an intravenous injection and the patient's neck is imaged with a gamma camera to show the location of all glands. A second image is obtained after washout time (approximately 2 hours), and the mitochondria in the oxyphil cells of the abnormal glands retaining the 99mTc are seen with the gamma camera. This imaging method will detect 75 to 90% of abnormal parathyroid glands in primary hyperparathyroidism (13-14). However, there is no clear evidence of the benefits of this method in secondary HPT. As there are no estimates of comparison between this method and the conventional exploring method in our region, the aim of this study is to compare the MIBI scintigraphy and ultrasonography in preoperative localization of secondary hyperparathyroidism.

Materials and Methods

The present study was conducted on secondary HPT patients' referred to the surgery ward of Shariati Hospital, Tehran, Iran (a referral teaching hospital of Tehran University of Medical Sciences). Through convenient sampling, 25 patients were enrolled into the study. The demographic and serologic (PTH, Ca, and P) data were collected from the medical records and inserted into a checklist. We evaluated each parathyroid gland separately. Forasmuch as every patient has 4 parathyroid glands on average, there were 100 glands to study. Patients with ectopic parathyroid glands were excluded from the study. We analyzed the results of MIBI scintigraphy and ultrasound for each gland separately and compared them with surgical localization as a gold standard. All patients underwent parathyroid MIBI scintigraphy and neck ultrasound. Each of the methods were performed by one single operator and interpreted by a single radiologist. Afterward, all patients underwent surgery and exploration was performed. Bilateral neck exploration was performed in all patients. All susceptible tissues were resected, weighted, and examined as a frozen section in the operation room by a single pathologist. The final positive results for parathyroid during surgery were considered as gold standard for the localization. All information was kept confidential and the patients signed consent forms.

Parathyroid scintigraphy

Dual phase scintigraphy scan (SS) was performed with a small field of view gamma camera (209 apex ELSCINT; General Electric; Milwaukee, WI) with a pinhole collimator. Moreover, 10 planar anteroposterior images (dynamic acquisition, Matrix 128*128) were obtained immediately after intravenous injection of 555 µBq 99mTc-methoxyisobutylisonitrile, sestamibi (early phase), and 2 hours later (late phase). A static image was taken of the thorax and mediastinum (300 seconds, Matrix 128*128, parallel collimator) to search for ectopic glands.

Ultrasonography

The patients were scanned lying supine with a pillow beneath the shoulders to slightly hyperextend the neck. Gray-scale imaging was performed with a high-frequency linear transducer (EUB-525 scanner; Hitachi, Japan). The study included longitudinal images extending from the carotid artery to midline and transverse images extending from the hyoid bone superiorly to the thoracic inlet inferiorly. An enlarged parathyroid gland on grey-scale imaging appeared as a hypoechoic or isoechoic (in few cases) nodule posterior or lateral to the thyroid lobe, but separated from it and not adherent to surrounding tissues, or within the thyroid parenchyma. Gray-scale imaging was supplemented by color and power Doppler imaging to look for feeding vessels and vascularity of suspected adenomas shown at initial gray-scale imaging. Color and power Doppler imaging commonly shows a characteristic extra-thyroidal feeding vessel (typically a branch of the inferior thyroidal artery), which enters the parathyroid gland at one of the poles. Internal vascularity is also commonly seen in a peripheral distribution.

Statistical methods

The data were entered and analyzed by SPSS for Windows (version 20; SPSS Inc., Chicago, IL, USA). The Quantitative and qualitative data are expressed by mean ± SD and n (%), respectively. Statistical tests such as t-test, chi-square, and correlation were performed. For testing the sensitivity and specificity, ROC curve analysis was conducted. Statistical significance was considered as P-value < 0.05.

Results

At the end of the study, the information of all 100 glands (25 patients) was analyzed, from which the male to female ratio was 13/12. Their age ranged between 16 to 72 years with mean age of 38 years. Mean Ca, P, AKP, and PTH were 10.41, 6.16, 526, and 1096 mg/dl, respectively (Table 1).

Table 1. Patients' characteristics and preoperative markers

Age (years)	38 (16-72)
Female to male ratio	13/12
Preoperative markers (mean)	
Preoperative Calcium (mg/dl)	10.4 (10.1 ± 0.8)
Phosphate (mg/dl)	6.16 (5.9 ± 0.7)
Parathyroid hormone (ng/L)	1096 (850 ± 270)
Alkaline phosphatase (IU/l)	526 (490 ± 120)

Scintigraphy

All patients underwent MIBI scintigraphy. MIBI scintigraphy was able to identify 45 parathyroid glands among 100 glands; therefore, MIBI scintigraphy had 47.3% sensitivity, 80% specificity, and 97.8% positive predictive value in detecting the glands.

Ultrasonography

On the other hand, preoperative ultrasonography was able to localize 64 parathyroid glands. In comparison to our gold standard (surgery), ultrasound had 69.5% sensitivity, 60% specificity, and 96.9% PPV.

When we analyzed both studies together, scintigraphy or ultrasonography localized 80 abnormal glands with 84.2% sensitivity, 80% specificity, and 98.7% positive predictive value (Table 2).

Table 2. Comparison between SS and US in secondary hyperparathyroidism

Method	Positive results	TP	FP	FN	PPV	Sensitivity
US	66 (66%)	64	2	31	96.9%	69.5%
SS	46 (46%)	45	1	50	97.8%	47.3%
US and SS	81 (81%)	80	1	15	98.7%	84.2%

TP: True Positive; FP: False Positive; FN: False Negative; PPV: Positive Predictive Value; SS: Scintigraphy Scan; US: Ultrasonography

Median weight of parathyroid glands in positive and negative localization ultrasonography was 1.6 gr (0.3-10) and 0.5 gr (0.3-3.6) which were significantly different in the two groups (P < 0.001). Mean Ca, P, ALP, and PTH in positive and negative ultrasonography were 9.7, 6.5 mg/dl, 682 IU/dl, and 1067 ng/dl vs. 9.3, 6.4 mg/dl, 481.6 IU/dl, and 1104 ng/dl, respectively, and did not have a significant difference (P = 0.15) (Table 3).

Median weight of parathyroid glands in positive and negative localization MIBI scintigraphy was 1.35 gr (0.3-10) and 0.5 gr (0.3-4) which were significantly different in the two groups (P < 0.001). Mean Ca, P, ALP, and PTH in positive and negative MIBI scintigraphy were 10.1, 6.3 mg/dl, 660.5 IU/dl, and 1240.5 ng/dl vs. 9.8, 6.6 mg/dl, 500.7 IU/dl, and 1069 ng/dl, respectively, and did not have a significant difference (P = 0.01) (Table 4).

Correlation test was performed for parathyroid glands' weight and serologic parameters, in which only Ca levels were significantly and positively correlated with parathyroid glands' weight (R = 0.321, P = 0.002).

Discussion

The use of routine preoperative localization study in patients with secondary hyperparathyroidism remains controversial. There are many options to use for localization, like scintigraphy, ultrasonography, CT, and MRI. However, only scintigraphy and recently ultrasonography have been used routinely. Among them ultrasonography is more available and cost-effective; nevertheless, it is operator dependent. Scintigraphy is a functional study while ultrasonography is an anatomical modality. Using them together improves preoperative localization (14).

In some recent studies, the usefulness of ultrasonography in primary hyperparathyroidism has been investigated. It has been shown that ultrasonography has as much sensitivity and specificity as scintigraphy in detecting parathyroid adenoma if performed by experienced radiologists (14). In our study, which was conducted between 2009 and 2012 on all included patients, MIBI scintigraphy and

Table 3. Serum calcium, serum parathyroid hormone, and weight of parathyroid glands in patients with secondary hyperparathyroidism according to the results by ultrasonographic localization

Parameters	Negative sonogram	Positive sonogram	P
Serum calcium (mg/dl)	9.3 (9 ± 0.7)	9.7 (9.8 ± 0.6)	N/S
Serum PTH (ng/L)	1104 (1150 ± 165)	1067 (1050 ± 130)	N/S
Weight of adenomas (gr)	0.5 (0.4 ± 0.2)	1.6 (1.3 ± 0.6)	< 0.001

Data shown are in median. NS, P > 0.05 by Student's t-test

Table 4. Serum calcium, serum parathyroid hormone, and weight of parathyroid glands in patients with secondary hyperparathyroidism according to results of scintigraphic localization

Parameters	Negative scintigram	Positive scintigram	P
Serum calcium (mg/dl)	9.8	10.1	N/S
Serum PTH (ng/L)	1069	1240	N/S
Weight of adenomas	0.5	1.35	0.001

Data shown are median. NS, P > 0.05 by Student's t-test ultrasonography were performed before surgery to localize the pathologic glands. Afterwards, all patients underwent bilateral neck exploration and total or 31/2 parathyroidectomy. The results indicate that the scan and ultrasound had 47.3% and 69.5% sensitivity, respectively. The PPV reported in our study was 97.8% and 96.9% for scintigraphy and ultrasonography, respectively. The combination of the two techniques yielded sensitivity of 84.2% and PPV of 98.7%. There was a statistically significant difference between the diagnostic accuracy of ultrasonography, scintigraphy, and “ultrasonography plus scintigraphy” as shown via comparison between two proportion version 8. The combination of scintigraphy and ultrasonography enhanced sensitivity when compared with either technique alone.

The sensitivity of ultrasound in our study was comparable to the studies of Ishibashi et al., Kasai et al., and Nishida et al (12,15,16). There are studies which demonstrate lower sensitivity compared to our study; this may be due to the sonologists’ experience and the difference between sensitivity of the units and the size of the glands. The MIBI scintigraphy sensitivity in our study was 47.3%, which was similar to the studies of Fuster et al., Papanikolaou et al., and Sukan et al. and was lower comparing to a few studies (17,18,19) The results of MIBI scintigraphy is dependent on several factors, such as the type of hyperplasia (nodular or diffuse), the grade of proliferation, and the amount of mitochondria contained oxyphill cells in the glands, the weight of the glands, age, serum levels of Ca, PTH, and vitamin D, existence of thyroid nodules, and recently discovered, the amount of gene amplification and translation of proliferating cell nuclear antigen (PCNA) (15-19).

Regarding our study, the sensitivity of ultrasound is higher than MIBI scintigraphy and it seems that ultrasound by an experienced sonographist can be more reliable than MIBI scintigraphy in localizing the glands prior to surgery in secondary hyperparathyroid patients. Furthermore, if we combine these two modalities, the sensitivity increases to 84.2%. Early studies of Tc-sestamibi scanning in secondary hyperparathyroidism found that sensitivity was lower than 50%, indicating that imaging was of limited usefulness (20) However, these studies used double-phase scanning. Subtraction scanning has provided better results (21) In a recent study evaluating simultaneous acquisition of images with two radionuclides (Tc-sestamibi and 123-iodine), a technique that is not affected by patient movements, the sensitivity for localizing parathyroid glands was 90% (2).

MIBI is the current radionuclide procedure of choice for parathyroid localization. Although reasonably good results can be obtained with planar imaging, the use of pinhole collimation, and the performance of subtraction imaging and single-photon emission computed tomography (SPECT) improve the accuracy of the test. The parathyroid glands can be found anywhere from the angle of the mandible to the base of the heart, and therefore, this entire region should be included in the field of view. MIBI is most sensitive for detecting parathyroid adenomas; therefore, it is less useful in patients with secondary hyperparathyroidism, where the predominant lesion is hyperplasia. Finally and most importantly, parathyroid scintigraphy is a localizing procedure, not a diagnostic procedure. It should, therefore, be reserved primarily for patients with documented primary hyperparathyroidism (15-21) As our study depicted, ultrasonography has almost 70% sensitivity that is much higher than the sensitivity of scintigraphy (47.3%). Since ultrasonography is easier to perform and more accessible than scintigraphy, it is logical that it be performed preoperatively in secondary hyperparathyroidism.

In order to determine which factors may interfere the accuracy of ultrasonography and scintigraphy, we compared preoperative serum calcium level, serum intact PTH level, and parathyroid glands’ weight between those patients in which ultrasonography and scintigraphy correctly localized the glands vs. those undetected. Only glands weight was significantly correlated with localization study findings.

Conclusion

Our study demonstrated 47.3% sensitivity for MIBI scintigraphy and 69.5% for ultrasound. However, for better localization of the parathyroid glands, using both modalities at the same time is recommended.

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