Has double-phase MIBI scintigraphy usefulness in the diagnosis of hyperparathyroidism?

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Abstract The usefulness of double-phase parathyroid technetium-99m-MIBI scintigraphy for the detection of hyperplastic parathyroid tissue has been described. The aim of the present study was to establish the effectiveness of this new technique in the morphological and functional assessment of parathyroid glands in patients with different types of hyperparathyroidism. We performed 99mTc-MIBI scintigraphy (MIBI) and neck ultrasonography in 38 patients with primary (n = 16) or secondary (n = 22) hyperparathyroidism. All patients underwent surgical neck exploration, removing a total of 84 parathyroid glands. Before and after surgery, blood intact parathyroid hormone (iPTH) was measured peripherally in both the right and left internal jugular veins. In patients with primary hyperparathyroidism, ultrasonography showed one enlarged gland in 11 cases (69%), while MIBI was positive in 15 (94%) (including two ectopic glands). The sensitivity of MIBI (93%) was greater than that of ultrasonography (68%), with a similar specificity (100 and 97%, respectively). In patients with secondary hyperparathyroidism, there was a discrepancy between both imaging modalities in 29 glands (33%). The sensitivity of both techniques was similar (41 and 54%, respectively), with the same specificity (89%). There were more difficulties in detecting the upper than the lower pathological glands. MIBI reflected more accurately the functionality of the glands, and ultrasonography has a better correlation with the volume and weight. In conclusion, Tc-99m-MIBI scintigraphy is a good technique to identify parathyroid hyperfunctioning in cases of primary hyperparathyroidism and to detect ectopic glands, but it does not give significantly better results than conventional ultrasonography in patients with secondary hyperparathyroidism.

Key words: hyperparathyroidism; technetium-99m-MIBI

Introduction

The use of pre-operative imaging in patients with hyperparathyroidism remains controversial. A wide variety of imaging techniques have been proposed to localize either parathyroid adenoma or hyperplasia, but the sensitivity of the majority of them is too low to justify their routine use [1].

In recent years, 99mTc-sestamibi (MIBI) scintigraphy has been used for the localization of parathyroid glands as an alternative method to 201Te/99mTc subtraction scintigraphy [2]. MIBI is a lipophilic radiotracer that concentrates in the cells and inside the mitochondria through active transport and passive diffusion. In metabolically hyperactive cells, the number of mitochondrias is increased and, according to the degree of cellular activity, different MIBI uptakes can be observed [3].

Recently, a simplified approach to parathyroid scintigraphy using a double-phase procedure after i.v. injection of MIBI has been proposed [4]. After the injection (first or thyroid phase), MIBI concentrates in thyroid and parathyroid tissues; in the second or parathyroid phase, its activity decreases in the normal thyroid while residual uptake persists in the presence of parathyroid adenomas or hyperactive tissue. This new technique seems to be sensitive enough to detect parathyroid adenomas, but this procedure has not been evaluated sufficiently in other parathyroid conditions.

Our aim was to establish the effectiveness of double-phase MIBI scintigraphy in the morphological and functional assessment of parathyroid glands in patients with different types of hyperparathyroidism.

Subjects and methods

Patients

The study group included 38 patients with clinical symptoms and biochemical parameters of hyperparathyroidism scheduled for surgical parathyroidectomy. Sixteen had primary
hyperparathyroidism (13 women and three men) and 22 (11 women and 11 men) secondary hyperparathyroidism.

Before surgical exploration, a MIBI scintigraphy and a parathyroid ultrasonography were performed in all patients. During surgery, just before dissecting the parathyroid glands and 15 min after excision of the pathological tissue, circulating intact parathyroid hormone (iPTH) was measured peripherally and in both the right and left internal jugular veins.

**Neck ultrasonography**

The ultrasonography study was performed with a 7.5 MHz duplex-Doppler (colour) transducer, with the patient in the supine position with hyperextension of the neck. The ultrasound examination (axial and longitudinal scans) included the thyroid region and the areas above and below the thyroid gland, to identify the parathyroid glands in even atypical locations. Normal parathyroid glands are not visualized with the equipment currently available. When pathological glands were observed, the echostructure (hypoechoic, homogeneous, inhomogeneous, calcifications) and size (longitudinal and anteroposterior diameters) were evaluated.

**Surgical evaluation**

All patients underwent bilateral surgical neck exploration, removing a total of 84 parathyroid glands. Criteria for surgery were independent of the MIBI and ultrasonography results. The volume of each gland was calculated according to the following formula: width \times length \times thickness \times 0.52. Histological examination of enlarged parathyroid glands was performed in all patients.

**99mTc-MIBI parathyroid scintigraphy**

The patients were injected i.v. with 740 Mbq (20 mCi) of 99mTc-sestamibi. The labelling efficiency was assessed previously by thin-layer chromatography. Radiochemical purity was >95% in all labellings.

Anterior views of the neck and the upper thorax were taken with the patient in the supine position. Images were obtained at 15 min (initial or thyroid phase) and 2 h (delayed or parathyroid phase) after the administration of the radiotracer. A digital gammacamera (Elscint SP4-HR) with a low-energy, high-resolution, parallel-hole collimator was used.

The scans were interpreted by two nuclear medicine physicians without previous knowledge of the patient’s data. Focal areas of increased uptake which showed either a relative progressive increase over time or a fixed uptake which persisted on delayed imaging were considered pathological. These areas were scored for activity on a three-point scale: 1 = faint uptake, 2 = moderate uptake, 3 = marked uptake.

**Statistical analysis**

Spearman bivariable correlation was used to calculate correlations between parameters. Mann-Whitney U and Kruskal-Wallis statistical tests were used to compare distributions between two or more groups. To adjust for repetitive testing (Bonferroni problem), we considered differences to be significant at the level of $P<0.05$. The comparison between the different diagnostic techniques was made by the exact calculation of binomial probability. Sensitivity and specificity were calculated by standard methods. A $P$ value <0.05 was considered statistically significant.

**Results**

**Biochemical data**

All patients had increased blood iPTH peripherally and in both right and left internal jugular veins, independently of whether they were suffering from primary or secondary hyperparathyroidism, although the levels were lower in primary hyperparathyroidism. After parathyroidectomy, these levels decreased in all cases (Table 1).

There was a positive correlation between the peripheral blood iPTH and that of both internal jugular veins ($P<0.01$). Blood iPTH tended to increase with the calculated volume of the parathyroid gland, and a positive correlation between the volume of the gland and the pre-operative levels of iPTH measured peripherally and in the jugular veins was also observed ($r=0.5$, $P<0.05$).

**Echographic and scintigraphic data**

In patients with primary hyperparathyroidism, parathyroid ultrasonography showed one enlarged gland in 11 patients (69%) and MIBI scintigraphy showed focal areas of increased uptake in at least one gland in 16 patients (100%), but one was a false positive and another one a false negative. In two patients with an ectopic gland, only the MIBI scintigraphy was able to localize them.

The sensitivity of MIBI scintigraphy (93%) was higher than the sensitivity of ultrasonography (68%), with a similar specificity (Table 2).

In patients with secondary hyperparathyroidism,
Double-phase parathyroid 99mTc-MIBI scintigraphy recently has been considered a good technique to locate hyperfunctioning parathyroid tissue [2,5], patients with higher iPTH had a marked tendency to incorporate tracer. However, there were no significant differences in weight between MIBI-positive and -negative glands; however, when only MIBI-positive glands were considered, a significant positive correlation between the uptake score and the gland's size was found \( (r=0.4, P<0.05) \).

There were more difficulties in detecting the upper than the lower pathological glands (Table 2). Also, there was a discrepancy between both imaging modalities in 29 glands (33%). In patients with secondary hyperparathyroidism, the sensitivity and specificity of both diagnostic techniques were similar but lower than in patients with primary hyperparathyroidism (Table 4).

**Discussion**

Many methods have been used for the diagnosis of both primary and secondary hyperparathyroidism. Some of these methods are not invasive, such as echography, computerized tomography, nuclear magnetic resonance or talium–pertechnetate scintigraphy. When these methods fail, some invasive procedures can be used (arteriography and selective venous cathetherism with iPTH measures). About 5–8% of surgical failures are due to the presence of ectopic glands not diagnosed by standard methods.

Although many parathyroid surgeons question the necessity of imaging before surgical exploration, the appropriate identification of all the pathological tissue is important in order to avoid future recurrences and surgical interventions.

Our study confirms that MIBI scintigraphy is a reliable imaging modality for locating parathyroid adenomas in patients with primary hyperparathyroidism, with a high sensitivity (93%) and specificity (97%). For the diagnosis of secondary hyperparathyroidism, the sensitivity of MIBI scintigraphy was greater than the sensitivity of ultrasonography, but both techniques were insufficient for the localization of all the pathological glands. Therefore, we agree with previous reports [7,12] that neither parathyroid MIBI scintigraphy nor ultrasonography are effective enough for the identification of multiglandular disease avoiding bilateral neck exploration.

The high discordance found in secondary hyperparathyroidism between MIBI scintigraphy and ultrasonography (33% of the glands) is not surprising. A relationship between the captation/elimination of MIBI and the number of mitochondria has been estab-
lished [9,11], explaining why 99mTc uptake and retention are higher in the abnormal parathyroid tissue [13]. According to our results, MIBI scintigraphy seems to reflect the functionality of the parathyroid gland more accurately, and the ultrasonography has a better correlation with the volume and weight of the glands.

Similarly to previous reports, our results show that MIBI scintigraphy was much more sensitive in diagnosing hyperfunctioning ectopic tissue.

In conclusion, 99mTc-MIBI scintigraphy is a good technique to identify hyperfunctioning parathyroid tissue in cases of primary hyperparathyroidism and to detect ectopic glands, but it does not give significantly better results than conventional ultrasonography in patients with secondary hyperparathyroidism.

In our opinion, MIBI scintigraphy can be used as the imaging technique of choice in the pre-operative localization of abnormal parathyroid glands in patients with primary hyperparathyroidism, but only as a complementary imaging technique in patients with secondary hyperparathyroidism. On the other hand, it may also be considered the best imaging option in all cases of recurrent hyperparathyroidism.

References