Original

The efficacy of low and high dose $^{99m}$Tc-MIBI protocols for intraoperative identification of hyperplastic parathyroid glands in secondary hyperparathyroidism

Esra Arzu Gencoglu*, Ayse Aktas

Department of Nuclear Medicine Baskent University Medical Faculty, Ankara, Turkey

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ABSTRACT

Objective: The aim of this study was to compare the efficacy of low- and high-dose $^{99m}$Tc-MIBI protocols for intraoperative identification of hyperplastic parathyroid glands via gamma probe in secondary hyperparathyroidism.

Material and Methods: This retrospective study was conducted using a prospective database of 59 patients who had undergone radioguided subtotal parathyroidectomy between 2004-2012. The patients were studied in 2 groups. Group 1 (n = 31) received 37 MBq $^{99m}$Tc-MIBI intravenously in the surgical room approximately 10 min before the beginning of the intervention and surgery was performed under gamma probe guidance. Group 2 (n = 28) received 555 MBq $^{99m}$Tc-MIBI intravenously 2 h before surgery, which was also performed under gamma probe guidance. Intraoperative gamma probe findings, laboratory findings, and histopathological findings were evaluated together.

Results: Using acceptance of the histopathological findings as gold standard, sensitivity and specificity of intraoperative gamma probe for identifying hyperplastic parathyroid glands was 98% and 100%, respectively, in both groups.

Conclusions: In the light of these findings, it is concluded that the low-dose $^{99m}$Tc-MIBI protocol might be preferable for intraoperative identification of hyperplastic parathyroid glands in secondary hyperparathyroidism patients because it was observed to be as effective as the high-dose $^{99m}$Tc-MIBI protocol. Furthermore, the low-dose protocol does not have the disadvantages that are associated with the high-dose protocol.

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La eficacia de los protocolos de dosis baja y alta de $^{99m}$Tc-MIBI para la identificación intraoperatoria de las glándulas paratiroides hiperplásicas en el hiperparatiroidismo secundario

RESUMEN

Objetivo: El objetivo de este estudio fue comparar la eficacia de los protocolos de dosis baja y alta de $^{99m}$Tc-MIBI para la identificación intraoperatoria de las glándulas paratiroides hiperplásicas usando sonda gamma en pacientes con hiperparatiroidismo secundario.

Material y métodos: Este estudio retrospectivo se llevó a cabo utilizando una base de datos prospectiva de 59 pacientes que habían sido sometidos a paratiroidectomía subtotal radioguiada entre 2004-2012. Los pacientes fueron examinados en 2 grupos. El grupo 1 (n = 31) recibió 37 MBq de $^{99m}$Tc-MIBI por vía intravenosa en el quirófano aproximadamente 10 min antes del comienzo de la intervención y la cirugía se realizó guiada por la sonda gamma. El grupo 2 (n = 28) recibió 555 MBq de $^{99m}$Tc-MIBI vía intravenosa 2 horas antes de la cirugía, la cirugía también se realizó guiada por la sonda gamma. Los hallazgos de sonda gamma intraoperatoria, los hallazgos histopatológicos de los pacientes fueron evaluados juntos.

Resultados: Aceptando los hallazgos histopatológicos como el estándar de oro, la sensibilidad y la especificidad de la sonda gamma intraoperatoria para identificar las glándulas paratiroides hiperplásicas fue 98 y 100%, respectivamente, en los 2 grupos.

* Corresponding author: Baskent University Medical Faculty, Department of Nuclear Medicine, Fevzi Çakmak Caddesi, 10. Sokak, No:45, 06490, Bahçelievler, Ankara, Turkey.
Tel.: +903122126868-1436, fax: +90 3122373333.
E-mail address: arzugencoglu@yahoo.com (E.A. Gencoglu).

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Introduction

Secondary hyperparathyroidism (SHPT) is characterized by an increase in production of parathormone (PTH) due to stimulation of the parathyroid glands by external factors, and consequent hyperplastic change in the glands. The most common factor associated with SHPT is chronic renal failure (CRF). Idiopathic hypercalcemia, hypermagnesemia, rickets, osteomalacia, malnutrition, and osteoporosis together with a decrease in active vitamin D can also cause SHPT, but less commonly.1–3

SHPT develops in patients with CRF due to the presence of metabolism disorders of calcium (Ca), phosphate (P), and vitamin D. Hyperphosphatemia, which occurs as a result of P retention, insufficient Ca absorption in the intestines due to disruption in the metabolism of vitamin D, change in the feed-back mechanism between the serum Ca level and PTH, resistance of the skeletal system to the calcemic effect of PTH, and a decrease in destruction of PTH due to renal dysfunction, leads to SHPT in patients with CRF.3–5

Although Ca, vitamin D, and anti-phosphorus drugs are initially sufficient in the treatment of SHPT in CRF patients, surgical treatment is eventually required. Studies have shown that parathyroidectomy is needed in 9.2% of patients within 10–15 years of the onset of CRF, and in as many as 20.8% after 16–20 years.6 Subtotal parathyroidectomy and total parathyroidectomy with autotransplantation are established surgical procedures for patients with refractory and symptomatic SHPT. Subtotal parathyroidectomy involves resection of three and a half glands and approximately 50 mg viable tissue is left in situ with preserved vascularity. Total parathyroidectomy with autotransplantation involves removal of all parathyroid glands and parts of the parathyroid gland that have been excised finely are placed in different regions of the brachio-radial muscle in the forearm.7

However, independent of the type of surgical procedure, the rate of persistent and recurrent disease is high (2%–12% and 10%–30%, respectively) in patients with SHPT in the postoperative period, due to the inability to observe all of the parathyroid glands during surgery and the inability to remove them all, especially in patients with a higher than normal number of parathyroid glands or in those with ectopic parathyroid glands. Re-surgery in patients with recurrent or persistent SHPT is in most cases unsuccessful because of high morbidity and complication rates, and prolonged surgical duration and technical difficulty.6,7

In an effort to increase the initial surgical success rate and reduce the rate of postoperative persistent or recurrent disease, use of intraoperative gamma probe has recently become more commonplace in SHPT patients. In this method, the localization of the pathologic parathyroid glands is determined by radioactivity counting with a portable gamma probe on the patient during the surgery. Use of an intraoperative gamma probe facilitates excision of the lesion, as it intraoperatively helps the surgeon identify the location of pathological parathyroid glands, resulting in less invasive surgery of shorter duration (especially in cases of ectopic parathyroid glands and parathyroid glands with a higher than normal number).4–10

Although the literature includes many studies on the identification of parathyroid lesions via intraoperative gamma probe in patients with primary hyperparathyroidism (PHPT), very few have investigated this in SHPT patients. In all studies that included patients with SHPT, the high-dose 99mTc methoxy isobutyl isonitrile (MIBI) protocol was used; 370–740 MBq 99mTc-MIBI was injected intravenously 1–3 h before the surgery, identification of pathological parathyroid glands was performed via intraoperative gamma probe, and surgical outcomes were positive.8–14 However, the high-dose 99mTc-MIBI protocol has some disadvantages, including a 1–3-h waiting period between 99mTc-MIBI injection and surgery, which negatively affects the scheduling of busy surgical suites. In addition, this long waiting period can decrease the gamma probe pathological parathyroid gland identification success rate due to a decrease in radioactivity retention in pathological foci over time. Because of these disadvantages of the long waiting period in the high-dose protocol, administration of 99mTc-MIBI immediately before starting surgery has been gaining in popularity. Furthermore, as 99mTc-MIBI is administered just before incision, a very low dose (37 MBq) of radioactivity (low-dose protocol) is sufficient for optimal identification of pathological foci; thus, the surgical team is exposed to less radiation than that associated with the high-dose regimen.15–18 The researchers calculated that the high-dose 99mTc-MIBI protocol exposes a surgeon to 0.05 mSv per patient; accordingly, the annual radiation exposure limit for a surgeon (surgeon and surgical suite personnel are considered non-radiation workers and are allowed an annual radiation dose limit of 1 mSv) would be reached after treating just 20 PHPT patients;19,20 however, with the low-dose protocol the annual radiation exposure limit would be reached after 400 such patients.21

The low-dose 99mTc-MIBI protocol has been used in patients with PHPT and successful outcomes were obtained (sensitivity: 96%–100%),15–18,21 however, to the best of our knowledge the literature does not include any studies on use of intraoperative gamma probe with the low-dose 99mTc-MIBI protocol in patients with SHPT. Therefore, the present study aimed to evaluate the usefulness of low-dose 99mTc-MIBI protocol in the intraoperative localization of hyperplastic parathyroid glands via gamma probe in patients with SHPT and to compare the efficacy of low-dose protocol and high-dose protocol.

Material and Methods

Patients

The study included data of 59 patients with SHPT due to CRF who had undergone subtotal parathyroidectomy via intraoperative gamma probe between January 2004 and December 2012. The data of patients were prospectively recorded in the database. Then, they were analyzed retrospectively. This study was approved by the Research Committee of our university, and all the patients were informed about the procedures and provided written informed consent.

All of the patients were in a hemodialysis program and none had previously undergone parathyroid surgery. Mean postsurgery follow-up was 13.8 months.

The low-dose 99mTc-MIBI protocol has been used successfully in patients with PHPT for identifying parathyroid lesions via intraoperative gamma probe at our hospital since 2000. Because of this positive clinical experience, the low-dose 99mTc-MIBI protocol is also used in addition to the high-dose protocol for identifying
Table 1
Demographic and preoperative laboratory data.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Female (%)</th>
<th>Male (%)</th>
<th>Preoperative PTH (ng L⁻¹)</th>
<th>Preoperative serum Ca (mmol L⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 31)</td>
<td>40 ± 10</td>
<td>11</td>
<td>20</td>
<td>1923 ± 623</td>
<td>2.4 ± 0.1</td>
</tr>
<tr>
<td>Group 2 (n = 28)</td>
<td>41 ± 14</td>
<td>18</td>
<td>18</td>
<td>1886 ± 617</td>
<td>2.4 ± 0.1</td>
</tr>
</tbody>
</table>

P value

n = Patient number
Data are given as mean ± standard error of the mean.

Table 2
Gamma probe results.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients identified 5 parathyroid glands</th>
<th>Number of patients identified 4 parathyroid glands</th>
<th>Number of patients identified 3 parathyroid glands</th>
<th>Total number of identified parathyroid glands via gamma probe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=31)</td>
<td>0</td>
<td>29</td>
<td>2</td>
<td>0 + (29 x 4) + (2 x 3) = 122</td>
</tr>
<tr>
<td>Group 2 (n=28)</td>
<td>1</td>
<td>25</td>
<td>2</td>
<td>(1 x 5) + (25 x 4) + (2 x 3) = 111</td>
</tr>
</tbody>
</table>

n = Patients number.

Table 3
Intraoperative gamma probe findings of patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>In vivo P:T ratio (range)</th>
<th>In vivo P:B ratio (range)</th>
<th>Ex vivo ratio (%) (mean ± standard error of the mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1.6 - 3.8</td>
<td>1.8 - 3.4</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>2.6 - 7.2</td>
<td>2.7 - 7.4</td>
<td>74 ± 22</td>
</tr>
</tbody>
</table>

Pathological parathyroid lesions via intraoperative gamma probe in patients with SHPT. The randomization method was used for the choice of low- or high-dose ⁹⁹ᵐTc-MIBI protocol application.

In the present study the patients were evaluated as 2 groups, according to the protocol used. Group 1 (n = 31) received 37 MBq ⁹⁹ᵐTc-MIBI (Polatom, Otwock, Poland) intravenously in the surgical suite approximately 10 min before incision and the surgery was performed via gamma probe guidance. Group 2 (n = 28) received 555 MBq ⁹⁹ᵐTc-MIBI intravenously 2 h before surgery, that was also performed under gamma probe guidance.

Intraoperative gamma probe findings, laboratory findings, and histopathological results were evaluated. Surgery was considered successful when the postsurgical PTH level was < 65 ng L⁻¹.

Radioguided Parathyroidectomy

Just before incision, background (thigh region) activity was recorded in each patient using an 11-mm diameter gamma probe (Europrobe, Eurorad, Strasbourg, France). Following incision, gamma probe radioactivity counts in suspected parathyroid lesions (in vivo and ex vivo) and in normal thyroid tissue (except the nodular area) were recorded. Radioactivity was also measured in the parathyroid lesion extraction site. When the in vivo suspicious parathyroid lesion radioactivity count/thyroid radioactivity count ratio (P:T) was ≥ 1.5, the in vivo suspicious parathyroid lesion radioactivity count/background radioactivity count ratio (P:B) was ≥ 2.5, and the ex vivo suspicious parathyroid lesion radioactivity count was > 20% of the background radioactivity count of the lesion extraction site, the excised lesion was considered pathological parathyroid tissue. All excised tissues were sent to the pathology department for frozen section analysis. When the excised tissue was confirmed to be parathyroid tissue in the frozen section analysis and the gamma probe radioactivity counts of the four quadrants were equalized, the surgical process was terminated. The excised parathyroid tissues were then evaluated histopathologically.

Statistical analysis

Data were analyzed using SPSS v.19.0 for Windows (SPSS, Inc., Chicago, Illinois, USA). Descriptive statistics were calculated and are shown as mean ± SD. Comparison of variables was performed using the paired t-test and Mann–Whitney U test. The level of statistical significance was set at P < 0.05.

Results

Patient characteristics

The demographic and preoperative laboratory data of patients (Group 1 and 2) are illustrated in Table 1.

There wasn’t a significant difference between the 2 groups in terms of preoperative findings (P > 0.05).

Gamma probe findings

Gamma probe results are summarized in Table 2. Accordingly, 122 pathological parathyroid glands of 31 patients were identified in Group 1 and 111 pathological parathyroid glands of 28 patients were identified in Group 2 via intraoperative gamma probe. However, 2 parathyroid glands in Group 1 and 2 were not observed.

In both groups, ectopic parathyroid glands were identified with intraoperative gamma probe. In total, 2 parathyroid glands in Group 1 were ectopic; 1 was localized in the carotid sheath and 1 was localized in the thymus. In Group 2, there were 3 ectopic parathyroid glands localized in the thymus. Thyrectomy was performed in the patients with a parathyroid lesion in the thymus, in addition to subtotal parathyroidectomy.

In vivo and ex vivo radioactivity ratios of patients in both groups were summarized in Table 3. The difference in these ratios between the 2 groups was not significant (P > 0.05).

Histopathological findings

Histopathological evaluation of the parathyroid lesions excised from the 31 patients in Group 1 and the 28 patients in Group 2 showed that 100% were hyperplastic parathyroid glands in both groups.

Mean weight of the excised glands was 456 ± 319 mg in Group 1 and 435 ± 332 mg in Group 2; the difference between groups was not significant (P > 0.05).

Based on acceptance of the histopathological findings as the gold standard the the sensitivity and specificity of hyperplastic parathyroid gland identification via intraoperative gamma probe was 98% and 100%, respectively, in both groups.

No false positive intraoperative gamma probe findings were noted.
Postoperative laboratory findings

In Group 1 in whom all of the pathologic parathyroid glands were detected (29/31 patients), the mean postoperative PTH level was 21 ± 6 ng L\(^{-1}\) and the postoperative mean serum Ca level was 2 ± 0.1 mmol L\(^{-1}\) on postoperative day 1. In Group 2 in whom all of the pathological parathyroid glands were detected via gamma probe (26/28 patients), the mean postoperative PTH value was 29 ± 5 ng L\(^{-1}\) and the mean postoperative serum Ca value was 2 ± 0.1 mmol L\(^{-1}\) on postoperative day 1. Statistical analysis showed that the postoperative serum PTH (P < 0.0001) and serum Ca (P < 0.001) levels were significantly lower than the preoperative levels in these patients. No clinical or laboratory findings indicative of recurrence were observed in these cases during the follow-up period.

However, postoperative laboratory findings remained high in 2 patients in both Group 1 and Group 2 in which only 3 of 4 parathyroid glands were identified during surgery. It was concluded that in these patients persistent hyperparathyroidism was associated with the parathyroid gland that was not identified via gamma probe and they were scheduled for re-surgery.

Discussion

As preoperative imaging methods cannot be used to guide surgery sufficiently,\(^{4,22-27}\) intraoperative localization via gamma probe has become more widespread in patients with hyperparathyroidism. With this method identification of pathologic parathyroid tissues is easier, surgery is less invasive, and surgical duration is reduced. In addition, small parathyroid lesions that uptake very little activity can be easily observed, as counting is performed via gamma probe after incision. Moreover, as the probe can be moved in all directions, ectopic parathyroid glands and glands localized deeply can be identified quickly and easily.\(^{28,29}\) Identification of parathyroid lesions via intraoperative gamma probe guidance is commonly used in patients with PHPT with successful results;\(^{19,20,28-30}\) however, there are few studies in the literature on the use of intraoperative gamma probe in SHPT.

In a study Chen et al. administered 370 MBq 99mTc-MIBI intra- venously to 25 SHPT patients and performed surgery 1–2 h later; all hyperplastic parathyroid glands in all patients were identified via intraoperative gamma probe (100%).\(^9\) Jorna et al. administered 400 MBq 99mTc-MIBI intravenously 1–2 h before surgery in 25 SHPT patients.\(^12\) They reported that the sensitivity and specificity for identifying hyperplastic parathyroid glands via intraoperative gamma probe was 97% and 92%, respectively. Nichol et al. administered 370 MBq 99mTc-MIBI to 5 SHPT patients 1–2 h prior to surgery and via intraoperative gamma probe accurately identified all hyperplastic parathyroid glands in all patients (100%).\(^9\) Similar results were obtained in a few other studies.\(^10,11,13\)

As noted above, hyperplastic parathyroid gland identification via intraoperative gamma probe was performed using the high-dose (370–400 MBq) 99mTc-MIBI protocol in all the studies related to SHPT; however, administration of a low dose (37 MBq) of 99mTc-MIBI immediately before surgery (low-dose protocol) in patients with hyperparathyroidism has been attracting more attention in recent years because of the disadvantages of the high-dose 99mTc-MIBI protocol, including a 1–3-h waiting period between injection and the onset of surgery, and exposure of the surgical team to high doses of radiation, though within acceptable limits. The Italian Study Group on Radioguided Surgery and Immunoscintigraphy (GISCRIS) has performed some studies on use of the low-dose 99mTc-MIBI protocol for identifying parathyroid adenomas via intraoperative gamma probe in patients with PHPT. In those studies the successful intraoperative identification rate via gamma probe was 96%–98%;\(^15,21\) however, to the best of our knowledge no study has examined the low-dose 99mTc-MIBI protocol in patients with SHPT.

In the present study the efficacy and usefulness of the low-dose 99mTc-MIBI protocol for identifying hyperplastic parathyroid glands via intraoperative gamma probe in patients with SHPT was examined for the first time, and the findings were compared with those obtained in patients with the high-dose 99mTc-MIBI protocol. The low-dose 99mTc-MIBI protocol was applied to the 31 patients (Group 1) and the high-dose 99mTc-MIBI protocol was administered to the 28 patients (Group 2). This study showed that there wasn’t a difference in the success rate in patients with SHPT between the low-dose and high-dose 99mTc-MIBI protocols. The sensitivity and specificity for identifying hyperplastic parathyroid glands via gamma probe was 98% and 100%, respectively, in both groups. The present findings in the high-dose 99mTc-MIBI protocol group were compatible with those of the above-mentioned studies in which the high-dose protocol was used;\(^8-14\) however, as the present study is the first to evaluate the low-dose 99mTc-MIBI protocol in SHPT patients, our findings in the low-dose 99mTc-MIBI protocol group could not be compared to those of other studies.

Intraoperative gamma probe has the highest superiority in identification of parathyroid glands that are more than usual and ectopic parathyroid glands as well. As in other studies,\(^3,10,12,14\) in the present study this method was successful in both groups. In Group 1 (low-dose 99mTc-MIBI protocol) 2 parathyroid glands were ectopic (1 was localized in the carotid sheath and 1 was localized in the thymus). In Group 2 (high-dose 99mTc-MIBI protocol), 3 ectopic parathyroid glands were identified in the thymus. Furthermore, in 1 patient (in Group 2) 5 parathyroid glands were identified via intraoperative gamma probe.

In the present study, as in others, to increase the sensitivity and specificity of intraoperative gamma probe-guided surgery for identifying hyperplastic parathyroid glands some important radioactivity measurements/ratios were used. The first was the 20% rule described by Murphy and Norman, in which the ex vivo surgical specimen count is >20% and occasionally > 50% of the background radioactivity count at the lesion extraction site; it is a reliable indicator that a pathological parathyroid gland was identified and excised.\(^29\) This ratio is useful for differentiating parathyroid tissue from other tissues, such as fat, lymph nodes, and the thymus. In a study by Jorna et al., the 20% rule was used and the ex vivo count ratio was > 20% in 101 of 104 hyperplastic parathyroid glands.\(^12\) There were 2 false-positive results (due to inflammation in the thyroid nodule) and 3 false-negative results. Chen et al. studied patients with SHPT using the 20% rule and reported a 100% accuracy rate.\(^3\) The others reported that the ex vivo count ratio was >20% in all hyperplastic parathyroid glands in patients with SHPT.\(^11,14\) In the present study use of the 20% rule showed that the ex vivo count ratio was >20% for all hyperplastic parathyroid glands in the patients in both groups (74% ± 22% in Group 1 and 78% ± 26% in Group 2), which is similar to the above mentioned studies.\(^9,11,12,14,29\) No false positive results were noted in either group in the present study.

Other gamma probe criteria that we utilized in both groups in the present study were in vivo P:T ratio and P:B ratio. It is known that an in vivo P:T ratio > 1.5 and a P:B ratio > 2.5 are strongly indicative of a pathologic parathyroid gland;\(^4,15-21\) however, to the best of our knowledge these criteria have not been used in any study on SHPT patients, although they have been used commonly in studies on PHPT patients. In the present study the in vivo P:T ratio was 1.6–3.8 and the P:B ratio was 2.6–7.2 in Group 1, versus 1.8–3.4 and 2.7–7.4, respectively, in Group 2, which is compatible with the findings of earlier studies on the low-and high-dose 99mTc-MIBI protocols in PHPT patients.\(^15,28-30\) Based on the present findings,
we think that it is beneficial to use the P:T and P:B ratios in addition to the 20% rule for identifying pathological parathyroid tissue via intra-operative gamma probe in patients with SHPT, as it is in patients with PHTH.

In the present study the low- and high-dose \(^{99m}\)Tc-MIBI protocols were also compared in terms of cost and duration of surgery. There wasn’t a difference in mean surgical duration or instrumentation cost between the 2 groups; however, in terms of radiopharmaceutical costs, the low-dose protocol was much less expensive than the high-dose protocol, as the MIBI kit was already prepared daily for myocardial perfusion scintigraphy and parathyroid scintigraphy: the cost of the 37 MBq \(^{99m}\)Tc-MIBI protocol was negligibly low.

**Conclusion**

The low-dose \(^{99m}\)Tc-MIBI protocol is a better option for intra-operative identification of hyperplastic parathyroid glands in SHPT patients, as it was as effective as the high-dose \(^{99m}\)Tc-MIBI protocol. Furthermore, in contrast to the high-dose protocol, the low-dose \(^{99m}\)Tc-MIBI protocol does not require an extended waiting period after radiopharmaceutical injection and surgical team exposure to radiation is much lower. In addition, the radiopharmaceutical cost is much lower than that of the high-dose protocol.

**Conflict of interest**

The authors declare no conflict of interest.

**References**