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

A R T I C L E   I N F O

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A B S T R A C T

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

R E S U M E N

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.
**Conclusions:** A la vista de estos resultados, se concluye que el protocolo de dosis baja de $^{99m}$Tc-MIBI puede ser preferible para la identificación intraoperatoria de las glándulas paratiroideas hiperplásicas en pacientes con hiperparatiroidismo secundario, porque se observó que era tan eficaz como el protocolo de dosis alta de $^{99m}$Tc-MIBI. Además, el protocolo de dosis baja no tiene las desventajas que se asocian con el protocolo de dosis alta.

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radiological parathyroid lesions via intraoperative gamma probe in patients with SHPT. The randomization method was used for the choice of low-or high-dose $^{99m}$Tc-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 $^{99m}$Tc-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 $^{99m}$Tc-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$^{-1}$. ¹⁴

Radioguided Parathyroidectomy

Just before incision, background (thigh region) activity was recorded in each patient using an 11-mm diameter gamma probe (Europaee, 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. ⁴ 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. Thymectomy 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.

### Table 1

Demographic and preoperative laboratory data.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 31)</th>
<th>Group 2 (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40 ± 10</td>
<td>41 ± 14</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>10</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
<td>18</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Preoperative PTH (ng L$^{-1}$)</td>
<td>1923 ± 623</td>
<td>1886 ± 617</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Preoperative serum Ca (mmol L$^{-1}$)</td>
<td>2.4 ± 0.1</td>
<td>2.4 ± 0.1</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

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 parathyroid glands</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 parathyroid glands</td>
</tr>
</tbody>
</table>

n = Patients number.
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, 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. Identification of parathyroid lesions via intraoperative gamma probe guidance is commonly used in patients with PHPT with successful results. 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 intravenously 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%). Jorna et al. administered 400 MBq ⁹⁹mTc-MIBI intravenously 1-2 h before surgery in 25 SHPT patients. 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%). Similar results were obtained in a few other studies.

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 (GISCRI) 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%; 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 given 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; 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, 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. 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. They reported that the ex vivo count ratio was > 20% in all hyperplastic parathyroid glands in patients with SHPT. 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. 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; 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. 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 PHPT.

In the present study the low- and high-dose 99mTc-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 99mTc-MIBI protocol was negligibly low.

Conclusion

The low-dose 99mTc-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 99mTc-MIBI protocol. Furthermore, in contrast to the high-dose protocol, the low-dose 99mTc-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