INTRAOPERATIVE PARATHORMONE ASSAY AND RADIO-GUIDED PARATHYROIDECTOMY IN PATIENTS WITH PRIMARY HIPERPARATHYROIDISM

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The outcome of surgical treatment of primary hyperparathyroidism (PHP) is largely dependent on the radicality of the operation. This is sometimes difficult due to abnormal location of the glands. The use of intraoperative parathormone assay (IOPTH) and a handheld gamma-ray detector (HGRD) might influence the outcome of treatment.

The aim of the study was to assess the feasibility of intraoperative parathormone assay and handheld gamma ray detector in surgical treatment of primary hyperparathyroidism.

Material and methods. Prospective analysis of the treatment outcomes of patients with PHP undergoing surgery at the Dept. of General and Endocrine Surgery was accomplished. The patients were divided into two groups: G1 – patients in whom HGRD was used to intraoperatively locate the parathyroid glands; G2 – patients in whom both the HGRD and IOPTH were utilized. In all of the patients preoperative serum calcium and PTH measurements were taken. Thirty minutes before the scheduled start of the operation, patients from both groups received an 800 MBq dose of the Tc-MIBI radiomarker. Gamma radiation measurements were performed with the use of a Gamma Finder handheld device. In patients from the G2 group, serum PTH was assessed 10 minutes after the removal of the last gland. In the G1 group, bilateral neck exploration was performed. In the G2 group, the operation was brought to a close after the Miami criterion was met; in most cases, the surgery was limited to unilateral neck exploration.

Results. Between 2007 and 2009 25 patients underwent surgery for PHP (group G1 – 12, group G2 – 13). There was one case of persistent hyperparathyroidism in group G1. All of the parathyroidectomies in group G2 were successful. No difference in the length of hospital stay were noted between the groups. The duration of surgery was longer in group G2.

Conclusions. Surgical treatment of PHP with the combined use of a handheld gamma radiation detector and an intraoperative parathormone assay yields satisfactory results despite limited tissue preparation.

Key words: parathyroidectomy, hyperparathyroidism, gamma radiation detector, intraoperative parathormone assay

Primary hyperparathyroidism (PHP) is a complex problem, requiring combined endocrinological and surgical treatment. According to epidemiological data, the occurrence of PHP is approximately 27-30/100 000 persons/year; the disease affects primarily elderly females (1, 2). Several possible factors are considered as causes of hyperparathyroidism, including mono – or polyclonal hyperplasia of parathyroid cells, single or multiple adenoma and parathyroid carcinoma. Successful surgical treatment must include meticulous removal of
all the altered glands (1). If the radicality of the procedure is insufficient, persistent hyperparathyroidism develops. Overly radical procedure results in postoperative hypocalcaemia (3).

The cornerstone of radical surgical treatment of PHP is the identification and removal of the altered glands. Despite the availability of advanced diagnostic techniques such as scintigraphy of computed tomography, reliable preoperative pinpointing of all of the glands is sometimes impossible (4, 5). Therefore, the need for a fast and reliable intraoperative method of parathyroid gland identification arose. Gamma radiation detectors (GRD’s) have been used for this end with increasing frequency (5). Being able to pinpoint the location of the glands decreases the need for wide neck exploration and therefore influences the incidence and severity of surgical complications (6).

Due to the many possible causes of PHP, an intraoperative test for the evaluation of the radicality of the surgery is necessary. Intraoperative parathormone level measurement (IOPTH) has been widely accepted for the task, despite ongoing dispute regarding its feasibility (7, 8, 9).

The aim of the study was to evaluate the value of intraoperative parathormone measurements and the use of a gamma radiation detector in patients undergoing surgery for primary hyperparathyroidism.

MATERIAL AND METHODS

The study group consisted of patients treated for primary hyperparathyroidism at the Department of General and Endocrine Surgery of the Nicolaus Copernicus University School of Medicine in Bydgoszcz, Poland. The authors performed a prospective analysis of the treatment outcomes of subsequent patients undergoing surgery for hyperparathyroidism between January 2007 and March 2009. The study group included 25 patients (20 females, 5 males, mean age 53 yrs, SD ± 13.2). Only patients with primary hyperparathyroidism were enrolled. Patients with secondary, tertiary or recurrent hyperparathyroidism were excluded from the study group. The results were analysed in the following groups:

– group one (G1) – patients undergoing surgery with the use of a gamma radiation detector; n=12,
– group two (G2) – patients in whom both the GRD and intraoperative parathormone assay were used; n=13.

The authors’ department has had use of a handheld gamma ray detector since 2007. For logistical reasons, IOPTH has been available since 2008. The availability of both diagnostic modalities in the years 2007-2009 was the criterion for patient enrolment into the two study groups.

Preoperative diagnostics and qualification for surgery was identical in both groups. The diagnosis was based on clinical examination, serum parathormone and calcium levels, parathyroid ultrasound and two-phase scintigraphy performed as an outpatient procedure. Preoperative preparation included laryngeal evaluation with the assessment of the vocal cords. All of the patients had serum calcium and parathormone levels taken one day prior to surgery; these were repeated during follow – up visits 3 and 6 months after discharge. Comorbidities are presented in tab. 1.

On the day of the surgery, the patients received an intravenous injection of an 800MBq (21.6 mCi) dose of the $^{99m}$Tc-MIBI radioisotope, followed by a scintigram taken after 30 min, after which the patient was transferred to the operating theater. Considering the time required for the induction of anesthesia, the procedure was started after a mean period of 75 ± 15 min from the injection of the radiopharmaceutical agent.

All procedures were performed by the same surgeon (J.P.). In patients from the G1 group, Bilateral Neck Exploration (BNE) was routinely performed via an incision at the base of the neck. A handheld gamma radiation detector (Gamma Finder; World of Medicine AG, Ludwigsstadt, Niemcy) was used for intraop-

Table 1. Comorbidities in patients treated for PHP

<table>
<thead>
<tr>
<th>Name</th>
<th>G1 (n=12)</th>
<th>G2 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>HCV</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Porphyria</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Nodular goiter</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
erative localization of the glands. The removed tissue was considered the causative factor of PHP if the radiation measured outside of the surgical field was at least 20% of the value measured within the neck. Intraoperative histological evaluation was not performed; all of the removed tissue underwent a postoperative histological evaluation.

The protocol of radioisotope administration and intraoperative radiation detection was the same in the G2 group. Additionally, serum parathormone levels were taken before the commencement of the surgery and intraoperatively, 10 min after the removal of the altered gland. PTH levels were measured using an immunoenzymatic microparticle assay with the CMIA chemoluminescent marker, by a quantitative method in Architect and System analyzers.

The procedure was considered radical if a decrease in PTH levels of at least 50% was observed (Miami criteria). If that was the case, further neck exploration was considered unnecessary and the procedure was concluded.

In some of the patients, additional procedures such as partial or total thyroidectomy had to performed due to a coexistent disease of the thyroid gland.

After surgery, serum calcium levels were taken in all of the patients, and any deficiency was corrected. Routine substitution of 6g calcium was used on the first postoperative day. Postoperative evaluation of the vocal cords was limited to cases with hoarseness or laryngeal wheezing. After discharge, the patients were called in for physical examination at 2 weeks, and at 3 and 6 months for examination and lab tests (calcium and parathormone levels).

The results were subjected to a statistical analysis using the Shapiro – Wilk normality test, the Manna-Whitney U test and the Friedman ANOVA test for non – normal variables. In cases where the class size in four – field tables was less than 6, Fisher’s exact test was used.

RESULTS

Only one case of persistent hyperparathyroidism was observed; it was in a patient from the G1 group.

The mean radiation in the surgical field was 1332 MBq (SD ± 455.8) in group G1 and 1243 MBq (SD ±401.1) in group G2; the difference between these values was not statistically significant (p=0.57). The mean radiation emitted by the excised tissue, measured outside the surgical field was 31%, of the value measured in the surgical field in G1 and 40% in G2; p=NS. In group G1, six of the removed specimens did not meet the criterion of 20% of radionuclide activity outside the surgical field compared to radiation measured within the surgical field. In group G2 this was true for one specimen.

Preoperative serum PTH levels were similar in both groups (p=0.4; tab. 2). In G2, the mean IOPTH concentration was 114 pg/ml. Even though this parameter did not reach reference values, it was still decreased by 75% from the initial value; thus, the Miami criterion was met in all G2 patients. During follow-up, PTH levels returned to normal in all of the patients from group G2. PTH levels at the 3 and 6 month follow – up were significantly lower in G2 than in G1 patients.

The dynamics of the PTH level changes was analyzed for both groups before and after surgery, and significant differences were noted (fig. 1). Similarly, the difference between the PTH levels in G2 was significant if intraoperative levels were considered (fig. 2). Changes in calcium levels correlated with the above-described alterations in PTH levels. Postoperative serum calcium levels were significantly lower than preoperative values both for G1 and G2 (fig. 3).

G1 patients required postoperative calcium supplementation with a mean daily dose of 6.6 g; G2 patients received a daily average of 6.15 g (p=NS).

Postoperative histology findings were similar in both groups, most of them being single

<table>
<thead>
<tr>
<th>Ca2+ (mmol/l)</th>
<th>G1</th>
<th>G2</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperatively</td>
<td>2.70 ± 0.25</td>
<td>2.73 ± 0.23</td>
<td>p=0.728</td>
</tr>
<tr>
<td>After 3 months</td>
<td>2.31 ± 0.2</td>
<td>2.17 ± 0.12</td>
<td>p=0.034</td>
</tr>
<tr>
<td>After 6 months</td>
<td>2.32 ± 0.08</td>
<td>2.28 ± 0.11</td>
<td>p=0.49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PTH (pg/ml)</th>
<th>G1</th>
<th>G2</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperatively</td>
<td>281.1 ± 175.9</td>
<td>465.2 ± 404.3</td>
<td>p=0.4059</td>
</tr>
<tr>
<td>After 3 months</td>
<td>74.5 ± 74.9</td>
<td>34.04 ± 14.3</td>
<td>p=0.0003</td>
</tr>
<tr>
<td>After 6 months</td>
<td>55.4 ± 5.6</td>
<td>39.4 ± 14.1</td>
<td>p=0.0059</td>
</tr>
</tbody>
</table>
Intraoperative parathormone assay and radio-guided parathyroidectomy

Fig. 1. Serum PTH levels in the study groups: preoperatively and upon follow-up [log(pg/ml)]*

* Significant difference in PTH levels according to Friedman ANOVA; G1: p=0.0002; G2: p=0.00002. Values shown in graph have been logarithmised

Fig. 2. Changes in PTH levels in group G2 (pg/ml)*

* Significant difference in PTH levels according to Friedman ANOVA G2: p<0.00001

Fig. 3. Serum Ca$^{2+}$ in both groups: preoperatively and upon follow-up (mmol/l)*

* Significant difference in PTH levels according to Friedman ANOVA; G1: p=0.011; G2: p=0.00004

adenomas (Fisher test: p=NS; tab. 3). Three cases of parathyroid hyperplasia were found in G1; even though in two of those patients only 2 glands were removed, no recurrence of hyperparathyroidism was observed during follow-up. In the third patient, preoperative scintigraphy showed no pathologies, and the glands could not be identified intraoperatively even with the handheld gamma detector. Radiation levels at the suspected locations of the glands were no different from baseline. Only after meticulous bilateral exploration were 3 enlarged parathyroid glands found and removed. Despite that, upon follow-up elevat-ed serum PTH and calcium levels were observed. Persistent hyperparathyroidism was diagnosed and another scintigraphy was performed, revealing an ectopic parathyroid gland. Upon reoperation the gland was discovered in the posterior mediastinum, behind the esophagus on the right side. The use of GRD and IOPTH has facilitated pinpointing the gland and improved the radicality of the operation. Upon histological examination, nodular hyperplasia was found.

Hyperplasia was also seen in one of the G2 patients, who had been admitted for recurrent nodular goiter with coexistent clinical and biochemical signs of PHP. Neither preoperative scintigraphy nor ultrasound showed a definite pathology. In this patient, both GRD and IOPTH was used during surgery. Three glands were visualized, and the removal of 2.5 of those met the Miami criteria.

Multiple adenomas were found in one G2 patient, who was primarily admitted for a giant nodular goiter. The surgery consisted in

Table 3. Postoperative histological findings

<table>
<thead>
<tr>
<th></th>
<th>G1 (n=12)</th>
<th>G2 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single adenoma</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Multiple adenomas</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nodular hyperplasia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
thyroidectomy and excision of three enlarged parathyroid glands.

In one G2 patient parathyroid cancer was diagnosed along with nodules within one of the thyroid lobes. Even though the initial operation consisted of thyroid lobectomy and parathyroidectomy, after histopathological results were obtained the patient was reoperated and three-field lymphadenectomy was performed.

Aside from parathyroidectomy, thyroidectomy was performed in one G1 patient and in 3 G2 patients. Mean duration of the procedure was 74.1 minutes in G1 and 116.9 minutes in G2; this difference is statistically significant (p=0.0004) (fig. 4). Mean hospital stay was 6.04 (SD ±1.39) days; the difference between the groups was borderline significant (G1 vs G2: 5.6 vs 6.5 days; p=0.08).

The postoperative complications were typical for this kind of surgery. In one of the G1 patients unilateral paresis of the recurrent laryngeal nerve was observed; the sequelae disappeared completely after 3 months. In two G2 patients hematomas formed at the surgical site – both were successfully managed conservatively. In one G2 patient, signs of hypocalcemic tetany developed on the second postoperative day despite oral calcium supplementation.

DISCUSSION

The contemporary surgeon has at his disposal an ever-widening range of diagnostic tests and devices serving to evaluate the efficacy of the treatment of PHP (10). Due to the varying location of the glands, the efficacy of treatment is usually worse without these additional measures, and the extent of tissue preparation is greater (11). The presented paper, though concerns a relatively small group of patients, enables an evaluation of a gamma radiation detector and IOPTH. The most important parameter of the efficiency of the surgical treatment is the percentage of the cases of persistent or recurrent hyperparathyroidism. In case of ectopic localization or hyperplasia of the glands, they are difficult to locate and reoperation is more frequently needed (12). In such cases neither preoperative scintigraphy nor intraoperative GRD allow for precise pinpointing of all of the glands. The weight of the gland may also make locating it difficult (13). In our material, all of the patients from group G2 were effectively cured, while in group g1 one case of persistent hyperparathyroidism was observed. Ectopic location of the fourth gland and low accumulation of the radioisotope prevented a radical operation despite the use of a GRD. Histopathology revealed that the PHP was caused by parathyroid hyperplasia.

In all of the patients enrolled in this study, a high dose of the radiomarker was used (800 MBq), administered approximately 75 minutes before skin incision. In effect, a comparable baseline radiation was achieved in all of the patients. Similarly, the percentage of radiation emitted by the removed tissue outside of the surgical field was comparable in both groups (G1 vs G2: 31 vs 40%, p=0.24), even though six of the specimens removed from G1 patients did not ultimately meet the criterion of 20% of radionuclide activity away from the surgical field. This fact may correlate with the above-mentioned phenomenon of weaker accumulation of the marker in hyperplastic parathyroid glands. The ectopic tissue is most often located within the thymus, in the thymothyroid ligament and in the posterior mediastinum beyond the esophagus. Some authors advocate a thymectomy in patients, in whom it is difficult to locate the parathyroid glands – especially those undergoing surgery for secondary or persistent hyperparathyroidism (14).

One of the basic diagnostic criteria of PHP is the finding of elevated serum parathormone levels. This test is also used to evaluate the efficiency of the surgery and to monitor the patients in the postoperative period (11, 15, 16, 17). Both of our groups were homogenous

Fig. 4. Duration of surgery in both study groups (min)
Intraoperative parathormone assay and radio-guided parathyroidectomy with respect to preoperative parathormone levels. In all of G2 patients, intraoperative decrease in PTH levels was observed, in accordance with the Miami criterion. Upon follow-up at 3 and 6 months after surgery, PTH levels were significantly lower in G2 than in G1. This may be explained by a higher efficiency of the surgery assisted by IOPTH, as well as by the presence of three cases of thyroidec- tomy in this group.

A query of the current literature has shown a dependence between intraoperative decrease of PTH levels and better treatment outcomes in PHP patients. This is true both for the risk of recurrence and the signs of hypocalcaemia (18, 19). Despite that, some authors are of the opinion that in patients with a single adenoma, which can be located by ultrasound and / or scintigraphy – in other words, in patients easy to diagnose – IOPTH might be superfluous (20). In turn, IOPTH is recommended as a diagnostic standard in all of the reoperations for persistent or recurrent hyperparathyroidism (21).

Several factors may influence IOPTH levels, among them patient age, size of the adenoma and GFR (22). In patients with parathyroid hyperplasia, in whom preoperative PTH levels are below 100 pg/ml, the 50% drop in IOPTH does not always mean that the surgery is radical (23, 24). In our material, the expected IOPTH drop was achieved in all of the G2 patients – including those with hyperplasia.

Literature suggests that roughly 40% of patients after surgery for PHP may show elevated PTH levels while their serum calcium levels remain normal. Therefore, some authors consider routine PTH measurements during follow-up visits in normocalcemic patients superfluous (25). In our material, PTH level after 3 and 6 months from surgery were significantly lower in comparison with preoperative values. We have not observed elevated PTH levels in normocalcemic patients.

Searching for parathyroid glands within a post-surgery scar requires experience and carries a high risk of complications (26). If a patient had undergone thyroidectomy and is subsequently operated for hyperparathyroidism, overly radical surgery may lead to hypoparathyroidism. It is widely accepted that an intraoperative decrease in PTH level below 10 pg/ml may indicate the danger of hypoparathyroidism (27). In the material presented here, one G2 patient had undergone a thyroidectomy in the past. Upon parathyroidectomy, 2.5 glands were removed, leading to a decrease of IOPTH to 44.5 pg/ml (in accordance with the Miami criterion); after 3 months PTH was 16.6 pg/ml, and after six months – 19.3 pg/ml. No signs of hypocalcaemia were observed.

The use of GRD and IOPTH facilitates pinpointing the pathologies and assessment of the effects of its removal; operation time is decreased and the extent of neck exploration is smaller (11, 28). While comparing the duration of the surgeries in both groups, the authors have not confirmed that it was shorter in the IOPTH group; on the contrary, it was significantly longer. This seems to have been caused by the need to wait for the IOPTH results. Besides, in three G2 patients a simultaneous partial thyroidectomy had to be performed.

Our observations confirm that the use of a handheld gamma detection device enables elimination of unnecessary tissue preparation, decreasing the risk of complications. Serum PTH level measurement is a good method for intraoperative assessment of the efficacy of parathyroidectomy. In order to significantly shorten the duration of the procedure, PTH levels must be measured directly in the operating theater.

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COMMENTARY

The intraoperative search for the parathyroid glands responsible for hyperfunction might pose problems, in spite of the experience of the operating teams.

Preoperative parathyroid gland scintigraphy and ultrasonography examinations enable to localize the parathyroid glands responsible for primary hyperthyroidism.

The intraoperative search for the parathyroid glands by means of the „Gamma Finder” facilitates their disclosure in the operative field, and the intraoperative determination of the PTH level confirms the effectiveness of the operation.

The gamma camera is especially useful during surgery of patients with recurrent hyperparathyroidism, enabling to avoid the dangerous exploration of the patients’ neck.

The intraoperative use of the „Gamma Finder” is limited by the radiology regulations. In spite of the small dose of the isotope and short half-life, regulations recommend the protection of biological material, and proper waste management. The use of isotopes in the operating room arouses emotions, especially in case of secondary hospital staff, in spite of numerous training courses.

A significant facilitation of the above-mentioned is the close vicinity of the Department of Nuclear Radiology. Confirming the usefulness of the „Gamma Finder” in case of parathyroid gland surgery, I would like to point to the fact of the more and more common use of the camera, considering the localization of GEP-NET tumors, especially of the pancreas.

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