Minimally Invasive Parathyroidectomy: Are Auxiliary Methods Necessary?

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ABSTRACT

Objective: To determine the success rate of minimally invasive parathyroidectomies (MIPs) with preoperative scintigraphy and ultrasonography, and to assess whether these imaging modalities are sufficient.

Study Design: Observational study.

Place and Duration of Study: Department of General Surgery, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey between March 2017 and December 2019.

Methodology: Medical records of 61 patients, who underwent MIP to treat primary hyperparathyroidism, were examined. Age, gender, and pre- and postoperative calcium, parathormone, and phosphorus levels were obtained from patient records. For all patients, the parathyroid (PT) glands were localised, using ultrasonography and Tc-99m methoxyisobutylisonitrile (MIBI) scintigraphy.

Results: The average patient age was 56.89 ± 13.47 years. Of the patients, 83.6% (n = 51) were females. Localisation of the PT glands with preoperative scintigraphy had an accuracy rate of 100%. However, ultrasonographic localisation was unsuccessful in five patients. Adenomas were noted in 44 patients (72.1%), hyperplasia in 15 patients (24.6%), and neoplasia in two patients (3.3%). Serum parathormone and calcium levels were measured 24 hours after surgery, and were found to be significantly reduced compared to the corresponding preoperative levels (p <0.001). Hypocalcaemia developed in four patients (6.6%), two (3.3%) of which were symptomatic. After three months, persistent hyperparathyroidism developed in five patients (8.2%).

Conclusion: Parathyroid scintigraphy has been demonstrated to be the gold standard for the preoperative localisation of PT glands. In the absence of scintigraphy, ultrasound guidance is the next useful technique for PT gland localisation.

Key Words: *Minimal invasive parathyroidectomy, Parathyroid scintigraphy, Ultrasonography, Parathormone.*

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INTRODUCTION

Primary hyperparathyroidism is an endocrine disease in which bone and mineral metabolism deteriorate with the production of excessive parathyroid hormone (PTH) secretion. In the 1970s, after routine serum calcium tests became widely available and acceptable for use, this disorder became one of the most commonly diagnosed endocrine diseases.[1,2] Primary hyperparathyroidism is usually a benign disease, but increased blood calcium levels can cause life-threatening consequences.

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Because of these potential consequences, it is crucial to have an immediate and accurate diagnosis to allow rapid treatment. The curative treatment for primary hyperparathyroidism is surgical intervention, and the first successful parathyroidectomy was performed in 1925.[3] Bilateral neck exploration was the standard treatment for primary hyperparathyroidism until minimal invasive parathyroidectomy (MIP) surgery took place, parallel to advances in medical imaging and scintigraphy.[4]

Almost 90% of primary hyperparathyroidism cases present as solitary adenomas. MIP provides advantages such as achieving better cosmetic results with a smaller incision, shortening the durations of surgery and the subsequent hospital stay, achieving an early recovery, minimising recurrent laryngeal nerve damage, and decreasing complications such as postoperative hypocalcaemia. Additionally, MIP has an extremely high success rate, which is equal to that of the standard method. One of the most important factors affecting the success of MIP is the ability to precisely detect the location of the lesion using preoperative imaging methods.[5]

Primary hyperparathyroidism is diagnosed using various invasive and non-invasive diagnostic methods, the most important of which are parathyroid scintigraphy and ultrasonography.[6] The frozen section procedure is used by pathology, which confirms the removal of the parathyroid gland *via* auxiliary intraoperative methods.[7] Increased success rates of MIP have also been reported with the use of assistive methods, such as the use of gamma probe radio-guidance to help localise the adenoma during surgery, and intraoperative parathormone testing performed until the adenoma has been removed.[8]

The purpose of the present study was to evaluate the success rate of MIP with preoperative scintigraphy and ultrasonography in this hospital, and to assess whether these imaging modalities are sufficient, given the currently available alternatives, such as gamma probe radio-guidance.

METHODOLOGY

The medical records of 61 patients, who underwent MIP to treat primary hyperparathyroidism between March 2017 and December 2019, were retrospectively examined. Patients with multiglandular disease, recurrent and/or persistent primary hyperparathyroidism, or other accompanying thyroid diseases were excluded from the study. Age, gender, and pre- and postoperative calcium, parathormone, and phosphorus levels were obtained from hospital records. The patients' calcium and phosphorus levels were measured using an autoanalyser, and serum PTH levels (normal range 12-88 pg/mL) were measured using chemiluminescence. The type of anaesthesia and the duration of the operation (the total time from introduction of anaesthesia to the closure of the skin incision) were recorded. After a primary hyperparathyroidism diagnosis, based on increased serum calcium and parathormone levels, all patients underwent ultrasonography and Tc-99m methoxyisobutylisonitrile (MIBI) and dual-phase parathyroid scintigraphy to localise the PT glands. All patients were evaluated pre- and postoperatively *via* direct laryngoscopy to assess the condition of the vocal cords. Ultrasonography was performed as follows: the procedure was performed by an experienced endocrine radiologist with a grey-scale, real-time ultrasound machine (General Electric Logiq E9, USA), equipped with a 7.5 MHz high-frequency linear transducer, with the patient in a supine position with cervical hyperextension. To obtain a high quality parathyroid scintigraphy, after the injection of 10 mCi Tc-99m MIBI (Polatom, Poland), static images were taken with the gamma camera (e-Cam, Siemens) at 15 minutes and 3 hours post-injection, to include the neck and mediastinal area in an anterior position. In both sets of images, ongoing focal retention was considered as a positive indicator for parathyroid pathology.

All surgeries were performed by the surgical endocrinology team. The frozen section procedure was performed for all patients. Drains were not placed at the surgical site.

Postoperative serum calcium, parathormone, and phosphorus levels were measured after 24 hours. Serum calcium and parathormone tests were repeated three months after the surgery.

For recording data of all patients, SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to test the normality of the quantitative data. Qualitative data were expressed as numbers and percentages, while quantitative data were expressed as mean ± SD and median (IQR). The Wilcoxon signed-rank test was used for comparisons, and statistical significance was defined as $p < 0.05$.

RESULTS

A total of 61 patients were included in the study. The average age was 56.89 ± 13.47 years. Of the patients, 83.6% (n = 51) were females and 16.4% (n = 10) were males. The median preoperative parathormone, calcium, and phosphorus values were: 148 (104.5-219.0) pg/mL, 11.3 (11.0-11.8) mg/dL; and 2.5 (2.3-2.95) mg/dL, respectively. The average surgical time was 46.2 ± 19.3 minutes (Table I). Patients' pathologies of the PT glands were located in the right upper gland in 1 (1.6%), lower right gland in 30 (49.2%), upper left gland in 5 (8.2%), and lower left gland in 25 (41%) by scintigraphy. PT glands were localised using scintigraphy in all patients; however, ultrasonography could not confirm the localisation in five cases, giving ultrasonography a success rate of 91.8% for localisation of the PT glands. The operative findings were correlated with scintigraphy, and based on the frozen specimen findings. The accuracy rate of PT gland localisation with preoperative scintigraphy was found to be 100%. None of the patients had postoperative wound infection, haematoma, and/or recurrent nerve damage.

Table I: Characteristics of the study population.

Parameters	n=61
Age (women/men)	56.61 ± 12.86/ 58.30 ± 16.98
Gender (women/men)	51 (%83.6) / 10 (%16.4)
Preoperative PTH	148 (104.5-219.0) pg/mL
Preoperative CA	11.3 (11.0-11.8) mg/dL
Preoperative P	2.5 (2.3-2.95) mg/dL
Anesthesia (general/local)	61/0
Duration of the surgery	46.2 ± 19.3 minutes

When pathology reports were reviewed, adenomas were documented in 44 patients (72.1%), hyperplasia in 15 patients (24.6%), and neoplasia in 2 patients (3.3%). The median postoperative parathormone, calcium, and phosphorus values were 46 pg/dL (30-82), 9.5 mg/dL (8.9-9.9), and 2.9 mg/dL (2.5-3.5), respectively. Postoperative serum parathormone and calcium levels were tested again after 24 hours, and were significantly reduced compared to preoperative serum parathormone and calcium levels ($p < 0.001$ for both). Hypocalcaemia developed in four patients (6.5%), 2 (3.3%) of which were symptomatic and were treated with 1-2 ml/kg of calcium gluconate.

After three months, the serum parathormone and calcium values for these patients were 68 pg/dL (39.0-94.5) and 9.4 mg/dL (9.1-10.0), respectively. These values were significantly lower than preoperative values ($p < 0.001$ for both). After three

months, persistent hyperparathyroidism developed in five patients (8.2%), and the parathormone and calcium values increased in these patients.

These patients underwent ultrasonography, scintigraphy, and single-photon emission computerised tomography (SPECT-CT). While no pathology was observed on ultrasonography. Scintigraphy demonstrated suspicious ectopic lesions in four patients, and a contralateral right lower lobe hyperplasia in one patient. The ectopic areas were found on SPECT-CT imaging to be the thymus, the retroesophageal area, the carotid carotid sheath (n = 2), and the contralateral right lower lobe. These patients subsequently underwent a second surgery. The pathological assessment of these four patients indicated recurrent adenomas, and one patient was diagnosed with hyperplasia.

DISCUSSION

MIP is currently the gold standard in the treatment for primary hyperparathyroidism. In recent years, the frequency of these surgeries has allowed for the development of additional preoperative imaging methods. Even when using a gamma probe for radio-guidance, intraoperative parathormone levels, frozen specimen pathology, scintigraphy, ultrasonography, SPECT-CT, and magnetic resonance imaging can all be used for pre- and postoperative evaluation. Some of these can even be used for intraoperative evaluation. Although ultrasonography and scintigraphy are the most common methods for preoperative PT gland localisation, there are ongoing studies assessing the value of adding other localisation methods.[6]

In the present study, the authors aimed to determine whether ultrasonography and scintigraphy are sufficient for successful surgery. The success rates of preoperative localisation with scintigraphy and ultrasonography were 100% and 91.8%, respectively. Given the results of the present study, the authors would advise using these inexpensive and widely available tests for preoperative assessment.

Ultrasonography is a cheap, non-invasive, and radiation-free imaging modality, and is readily available.[9] As there is an operator-dependent aspect for ultrasonography, sensitivity varies from 33-92%, which could be considered a disadvantage.[10] Specialised radiologists, endocrinologists, or endocrine surgeons can perform the ultrasonography, potentially with an increased rate of accuracy for the detection of disease. Predictably, localisation becomes easier as the adenoma increases in size,[11] which increases the success of preoperative imaging for localisation. In a previous study, Solorzano *et al.* found that 77% of preoperative localisation, performed correctly and with ultrasonography done by endocrine surgeons, was equally as successful as scintigraphy.[12] In this study, there were only five cases in which an experienced ultrasonography radiologist was unable to localise PT gland pathology.

Scintigraphy is one of the primary preoperative imaging modalities used to localise PT glands in clinical practise. In a meta-analysis involving 6,331 patients, Denham *et al*. found that the sensitivity of scintigraphy for parathyroid adenomas was 91%, and its specificity was 98.8%.[13] In cases where scintigraphy and ultrasonography are unable to localise lesions, the surgical success rate is significantly reduced.[14] Although the sensitivity of scintigraphy is lower in multiple gland pathologies; and in the presence of accompanying thyroid disease, these patients were excluded from the present study. Erbil *et al*. found that sestamibi scintigraphy, high-resolution ultrasonography, and a combination of both, have sensitivities of 96%, 100%, and 100%, respectively, when there are no nodules in the thyroid gland.[15] In the present study, localisation with scintigraphy was successful for all preoperative patients, and it is believed that the results of this study indicate that scintigraphy is sufficient for successful MIP.

Although ultrasonography and scintigraphy are considered to be the primary imaging modalities for preoperative PT gland localisation, computed tomography, magnetic resonance imaging, SPECT-CT, PET, and venous sampling are other methods which can be used in the recognition of glands in unusual locations. These methods can be used in cases of persistent and recurrent primary hyperparathyroidism, in which localisation with scintigraphy and ultrasonography are not successful.[16] The total success rate of ultrasonography and scintigraphy, prior to secondary operations, is over 85%.[17] In the present study, even though the sensitivity of scintigraphy correlated 100% with the surgical findings, five cases of persistent hyperparathyroidism and new lesions were successfully detected when imaged with SPECT-CT.

Frozen specimen pathology is the most important step to confirm the diagnosis of an adenoma. In a retrospective study of 1,579 cases, Westra *et al*. identified the overall accuracy of frozen specimen pathology as 99.2%.[18] In all of the patients included in the present study, the PT gland pathologies were diagnosed from frozen specimens. It is obvious that persistent hyperparathyroidism, caused by multiple glands, is not associated with frozen specimen pathology, which is preferred because it has the same or an even higher success rate; and it is cheaper than other methods of diagnosis.

Persistent hyperparathyroidism is usually related to parathyroid gland pathology that existed prior to the first surgery and which was not removed. It has been reported that there may be a 1-10% rate of recurrent hyperparathyroidism or a 2-22% rate of persistent hyperparathyroidism after treatment of the primary hyperparathyroidism. The most common causes of persistent and recurrent hyperparathyroidism are ectopic localisations and multiple glands.[19] In the present study, persistent hyperparathyroidism was detected in five patients (8.2%), four of whom had atypical placement, and one had a second adenoma on the contralateral side. The ratio of persistent hyperparathyroidism is consistent with and acceptable to current available literature. The rate of ectopic placement in the present study, persistent hyperparathyroidism patients was 80%.

Temporary hypocalcaemia could be a challenging clinical side

effect. In a previously published meta-analysis of 82 observational and six randomised studies, hypocalcaemia rates were reported as 2.3-13.6% after parathyroidectomy.[20] Typically, hypocalcaemia is treated with medical intervention and does not recur. Temporary hypocalcaemia was observed in four (6.6%) patients during the postoperative period of the present study, which is compatible with current available literature.

CONCLUSION

Observing very high success and low recurrence rates in the present study, it is shown that MIP with preoperative ultrasonography and/or scintigraphy does not require intraoperative imaging in patients with primary hyperparathyroidism. Current available literature, however, does indicate that intraoperative auxiliary methods may be needed in more complicated cases.

ETHICAL APPROVAL:

This study was conducted in compliance with the ethical principles, according to the Declaration of Helsinki; and it was approved by the local Institutional Review Board (KAEK: 27.05.2020/32).

PATIENTS' CONSENT:

Because this study was retrospective, the patients' consent was waived.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

HB, SY, ES, YK, MAB: Conceived the study design, involved in data collection, performed the statistical analysis, interpreted data and prepared the manuscript draft.

All the authors critically reviewed the final version of the manuscript and approved it for publication.

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