Original Research Article

THE USEFULNESS OF ^{99M}TECHNETIUM-SESTAMIBI PARATHYROID SCINTIGRAPHY IN PREOPERATIVE LOCALIZATION OF PARATHYROID ADENOMA IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM AT AN ACADEMIC HOSPITAL IN SOUTH AFRICA.

Abstract:

BACKGROUND: Primary hyperparathyroidism (PHPT) is an endocrine disorder with increased secretion of parathyroid hormone and elevated serum calcium level. Parathyroid adenoma is the most common cause. The introduction of preoperative localization of parathyroid adenoma using 99mTc-sestaMIBI has made parathyroid surgery minimally invasive. It becomes important to determine its usefulness in actual localization of parathyroid adenoma by correlating such with surgical and histological outcomes. METHODS: This is a retrospective evaluation which involved electronic data retrieval for patients with biochemical diagnosis of hyperparathyroidism who presented for parathyroid nuclear scan and subsequently had surgical resection and histopathological diagnosis at the UAH. A total of 11 patients were involved in this study. Data obtained was analysed. RESULTS: The mean age of the study group was a 55.82Â±15.46 year (age range of 29 years to 81 years) and females constituted 81.8% of the study group. The mean corrected calcium level was high preoperatively (2.93Â±0.5) but normalized post-operatively (2.29Â±0.3) ($p < 0.001$) while preoperative mean parathyroid hormone level was also high (26.86 Â±44.5) but normalized post-operatively (5.66Â± 2.2) ($p < 0.001$). All the 11 patients had positive 99mTc-Sestamibi scan for parathyroid adenoma and 27.3% of these patients had multiple (two) parathyroid adenomas. A total of 14 parathyroid adenomas were therefore detected. The surgeons detected and excised parathyroid adenomas at locations depicted by the 99mTc-sestamibi scan for all the eleven patients and 14 sites. All of the fourteen excised tissue were subsequently confirmed by histology to be parathyroid adenoma. CONCLUSION: Findings of this study showed accurate localization of parathyroid adenoma in all the patients as confirmed by surgery, histology and normalized post-operative corrected calcium and parathyroid hormone. Hence dual-phased 99mTc-sestamibi scintigraphy in the preoperative localization of parathyroid adenoma in patients with primary hyperparathyroidism at the Universitas Academic Hospital, Bloemfontein is a useful procedure.

Keywords:- Usefulness, 99mtechnetium-sestamibi, parathyroid, scintigraphy, preoperative localization, parathyroid adenoma, primary hyperparathyroidism

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a metabolic disorder characterized by abnormally increased secretion of parathyroid hormone (PTH) and elevated serum calcium levels as a result of a deficiency in the regulatory mechanism of parathyroid hormone release. There is increasing an incidence of primary hyperparathyroidism which may be related to the improvement in diagnostic capacity and increasing knowledge about the disease.[1]

Implicated in the etiology of primary hyperparathyroidism include parathyroid adenoma which constitutes 80%-85% of cases. The cause of most parathyroid adenomas is unknown. However, about 10 percent are thought to be hereditary or familial. Others are parathyroid hyperplasia involving more than 1 gland and usually all 4 glands contributing 10%–15% of cases and parathyroid carcinoma which is however rare contributing 0.5%–1% of all cases.[2] Women are twice as likely to develop parathyroid adenomas as men, and often after menopause with a Female: Male ratio of 7 : 3. Patients with PHPT are usually asymptomatic but may clinically present with non-specific symptoms such as fatigue, pain and weakness as well as polydipsia, polyuria, kidney stones, neuropsychiatric disease or bone involvement. Other symptoms they may present with include anorexia, nausea, vomiting, and constipation. Cardiac arrhythmias, depression or mental confusion, coma and death can occur. [3]

Neck exploration for possible detection and excision of the parathyroid adenoma(s) with further visualization and biopsy of the other glands were the standard traditional approach surgically for the management of primary hyperparathyroidism.[4] This had associated complications such as persistent and reoccurring primary hyperparathyroidism. Preoperative localization of parathyroid adenoma using Technetium (Tc) 99m sesta-methoxyisobutyl isonitrile (99mTc-sestaMIBI) helps to make surgery minimally invasive, thus avoiding cervical exploration.[5-6] It also significantly reduces the entire operative time, lowers the rate of associated complications and ultimately prevents or at least reduces the rate of recurrence of parathyroid adenoma.[5,7]

Globally, there is widespread use of unilateral or focused exploration in patients with parathyroid adenoma, hence making preoperative localization of the pathological hyperparathyroidism mandatory.[4,6,8] At the Universitas Academic Hospital (UAH), Bloemfontein, preoperative localization of parathyroid adenoma in patients with primary hyperparathyroidism is a procedure occasionally done and thus it becomes important to determine the usefulness of this procedure by using a dual-phased planar pinhole 99mTc-sestaMIBI method in localizing parathyroid adenoma pre-operatively at the UAH.

METHODS AND MATERIALS

This is a retrospective evaluation which involved patients with biochemical diagnosis of hyperparathyroidism who presented for a parathyroid nuclear scan and subsequently had surgical resection and histopathological diagnosis at the UAH. A total of 11 patients were involved in this study. There were 9 women and 2 men with an age range of 29 years to 81 years.

Data retrieval: All files of adult patients diagnosed with primary hyperparathyroidism who were referred to department of Nuclear Medicine, Universitas Academic Hospital Bloemfontein for localization of parathyroid adenoma were retrieved. The following were considered in retrieving data and any patient data that did not adhere to the under listed criteria were excluded

INCLUSION CRITERIA AND EXCLUSION CRITERIA: Data were then included if the patient met with all of the following criteria:

1. There was biochemical evidence of primary hyperparathyroidism using hypercalcaemia and parathyroid hormone level.
2. He or she underwent early and late planar pinhole 99mTc sestamibi scintigraphy imaging.
3. He or she underwent surgical removal of the parathyroid adenoma, including disease limited to the neck.
4. There was a histopathological evaluation by means of a frozen section, macroscopy and microscopy.

Preoperative laboratory evaluation: Patient data with elevated serum calcium corrected levels were retrieved for the purpose of this study. At the Universitas Academic Hospital, hypercalcaemia is confirmed by an elevated serum calcium level of greater than 2.56mmol/l (normal reference is 2.05-2.56 mmol/l). Patient's parathyroid hormone level was also retrieved and at UAH, the normal range is 1.6-6.9pmol/l. PHPT is characterized mainly by elevated serum calcium measurement with accompanied elevated or inappropriately high-normal PTH.[9] Nevertheless, a small percentage of patients with PHPT may have PTH values at the upper end reference range, which is inappropriately high in the presence of elevated serum calcium.[9]

99mTc-sestaMIBI parathyroid scintigraphy: Data of patients who had parathyroid scintigraphy at the Universitas Academic Hospital were obtained. Data showed that the patients were injected intravenously with 20mCi of 99mTc-MIBI and subsequently parathyroid imaging was performed using a gamma camera. Anterior planar images of the neck were obtained i.e patients had static images (15 minutes per image) using a pinhole collimator over the thyroid area at 30mins (early) and 2-4 hours (delayed) post injection.

Interpretation of 99mTc-sestaMIBI parathyroid scintigraphy: Interpretation of the 99mTc-sestaMIBI scans was done by the Nuclear Physician on duty at the time. Area(s) of increased focal uptake of activity in the thyroid gland which persisted on late imaging was considered positive for possible parathyroid adenoma unlike the thyroid gland uptake that progressively decreased with time (differential wash out). A hand-held gamma probe was used to identify the maximum activity count over neck area and subsequently marked on the skin.

Surgery: Following the detection of parathyroid solitary adenoma(s) on 99mTc-sestaMIBI, the eleven patients had minimally invasive excision of these parathyroid adenoma(s) performed under general anaesthesia. Prior to the surgical incision, a hand-held gamma probe was used to scan patient's neck and this was useful in identifying the area with highest radioactivity count and if it corresponded with the area of the skin marked. A small transverse cervical incision was made at the site and deepened. Then the gamma probe was used repeatedly in the incised area to guide the surgeon to the area of highest counts on the adenoma. Following the removal of the target tissue, there was measurement of the

118 radioactivity in the removed target tissue and the surgical area to confirm successful
119 removal of the adenoma. Successful surgery was defined as normal parathyroid hormone
120 and corrected calcium values in the post operative period.

121 **Post-operative laboratory evaluation:** Histo-pathological diagnosis was confirmed with the
122 help of intra-operative frozen section; macroscopy and microscopy at the histo-pathology
123 laboratory of the Universitas Academic hospital, Bloemfontein. A blood sample was drawn
124 for blood chemistry and postoperative serum calcium and parathyroid levels were
125 monitored in all patients at the Chemical Pathology Laboratory of the Universitas Academic
126 Hospital, Bloemfontein. At the Universitas Academic Hospital, the normal reference value
127 for serum calcium and corrected calcium is 2.05-2.56 mmol/l. Patient's parathyroid
128 hormone level was also retrieved and at UAH, the normal range is 1.6-6.9pmol/l.

129 **STATISTICAL DATA ANALYSIS**: Quantitative data were expressed as the means and standard
130 deviation and nominal data expressed as a percentage. A comparison between groups for
131 quantitative variables was performed using the t-test. Nominal variables were evaluated
132 using the $\square^2$ test. Significance assessed at $p<0.05$.

133 **ETHICAL CONSIDERATIONS:** Ethical clearance was obtained from University of Free State
134 Faculty of Health Sciences Ethical Review Committee (REC Reference nr 230408-011; IRB nr
135 00006240) after evaluation of the investigation protocol. Permission was also obtained
136 from the office of the Director of Clinical Services, the Universitas Academic Hospital
137 Bloemfontein, to use patient data for the purpose of this study.

138 **RESULTS**

139 Eleven patients met the inclusion criteria and hence were studied. These constituted the
140 study group.

141 **Age distribution of study group**

142 The mean age of the study group was 55.82±15.46 years with a range of 29 years to 81
143 years (Table1).

144 **Table1: Descriptive Statistics of age of study group**

n	Minimum (yrs)	Maximum (yrs)	Mean (yrs)	Std. Deviation
11	**29**	**81**	**55.82**	**15.46**

145

146 **Gender distribution of study group**

147 In this study, females constituted 81.8% of the study group while males made up the
148 remainder (Table 2).

149 **Table 2: Gender of study group**

Gender	n	% of total study group
Females	9	81.8
Males	2	18.3

150 **Results of Corrected calcium level of study group**

151 The mean corrected calcium level was high preoperatively (2.93±0.5) but normalized post-
152 operatively (2.29±0.3) and found to be statistically significant ($p < 0.001$). See Table 3.

153

154 **Table 3: Descriptive statistics of corrected calcium (mmol/l) level of study group**

Parameter	n	Minimum	Maximum	Mean	Std. Deviation
PRE-OPERATIVE	11	2.58	4.46	2.93	0.5
POST-OPERATIVE	11	1.58	2.54	2.29	0.3

155 p value <0.001

156

157 **Results of parathyroid hormone (pmol/l) level of study group**

158 The preoperative mean parathyroid hormone level was high (26.86 ±44.5) but normalized
159 post-operatively (5.66± 2.2) See Table 4.

160 **Table 4: Descriptive statistics of parathyroid hormone level of study group**

Parameter	n	Minimum	Maximum	Mean	Std. Deviation
PRE-OPERATIVE	11	5.0	159	26.86	44.5
POST-OPERATIVE	11	1.0	8.0	5.66	2.20

161 P value <0.001

162 **Results of 99mTc-Sestamibi parathyroid scintigraphy**

163 All 11 patients (100%) had a positive 99mTc-Sestamibi scan for parathyroid adenomas and 3
164 of these patients had multiple (two) parathyroid adenomas. A total of 14 parathyroid
165 adenomas were therefore detected, of which 9 were located in the left lobe of the thyroid
166 gland while 5 were found in the right lobe of the thyroid gland.

167 Of all the parathyroid adenomas detected in both lobes of the thyroid gland, 6 were located
168 in the inferior pole of the left thyroid lobe (see table 5).

169

170 **Table 5: Location of parathyroid enlargements in the thyroid gland**

Location	n	%
Left inferior pole	**6**	**42.9**
Right superior pole	**4**	**28.6**
Left superior pole	**3**	**21.4**
Right inferior pole	**1**	**7.1**
Total	**14**	**100**

Results of surgery: Intra-operatively, the surgeons detected and excised parathyroid adenomas at locations depicted by the 99mTc-sestaMIBI scan for all eleven patients and 14 sites. Intra-operative guidance with a hand-held gamma probe and adequate removal of hyper-functioning parathyroid tissue was possible in all the patients.

Results of histology All (100%) of the fourteen excised tissue samples were subsequently confirmed by histology to be parathyroid adenoma.

DISCUSSION

This section deals with the findings of this study regarding the usefulness of the dual-phased planar pinhole 99mTc-sestaMIBI scintigraphy in the preoperative localization of parathyroid adenoma in patients with primary hyperparathyroidism at the Universitas Academic Hospital, Bloemfontein. Eleven patients met the inclusion criteria and hence were studied. The age range of the investigation group was between 29 years to 81 years with mean age of 55.86 years. Females constituted 81.8% of the study group with males accounting for 18.2%. In the work done by several authors, it was discovered that the mean age and gender of the study group was consistent with the findings in this present study.[10-13]

It is important to note that the diagnosis of hyperparathyroidism is based on biochemical markers. PHPT is characterized mainly by elevated serum calcium measurement with accompanied elevated or inappropriately high-normal PTH.[9] Nevertheless, a small percentage of patients with PHPT may have PTH values at the upper end reference range, which is inappropriately high in the presence of elevated serum calcium.[9] In this study, all

191 the patients had elevated corrected serum calcium (with mean of ≥ 2.93 ±0.5 mmol/l)
192 preoperatively similar to the findings of Mshelia et al, the preoperative mean corrected
193 serum calcium and parathyroid hormone level found to be above the upper limit of normal
194 in this study, normalized post operatively.[14] This further strengthened the diagnosis of
195 PHPT.
196

197 Localization of parathyroid adenoma and their precise identification and excision during
198 surgery has always remained a challenge because of inconsistent location of the normal
199 parathyroid glands and the possibility of supernumerary ectopic glands. However in this
200 study, 99mTc-sestaMIBI dual-phased planar scintigraphy showed a 100% positive scan result
201 for parathyroid adenoma with multiple parathyroid adenomas found in about a third of the
202 patients giving a total of 14 sites of parathyroid adenoma. 99mTc-Sestamibi imaging
203 technique has been depicted by various authors to have a high degree of accuracy for
204 localization of solitary parathyroid adenomas preoperatively.[6,11] In this study, the surgeons
205 detected and excised parathyroid adenomas at locations depicted by the 99mTc-sestaMIBI
206 scan for all the eleven patients and 14 sites of parathyroid adenomas. Intra-operative
207 guidance with a hand-held gamma probe and adequate removal of hyper-functioning
208 parathyroid tissue was possible in all the patients. This correlates with the findings of some
209 other authors.[5,11,15,16] Combined SPECT/CT may increase localization of parathyroid
210 adenoma.

211 Appropriate localization and identification of these abnormal glands were confirmed by the
212 normalization of patient's parathyroid hormone and corrected calcium values following the
213 operative procedure.[15] Additionally, all (100%) of the fourteen excised parathyroid tissues
214 were confirmed by histology to be parathyroid adenoma consistent with the outcome of the
215 work by Stewart et al[15], where 94.2 % of patients had a histopathologic confirmation of
216 parathyroid adenoma with postoperative resolution of hypercalcemia and primary
217 hyperparathyroidism. There is the risk of post operative complications in patients who
218 under parathyroidectomy and the main complications are hoarseness due to injury to
219 recurrent laryngeal nerve, Hypocalcaemia and haematoma due to bleeding in the neck. To
220 avoid injury to the recurrent laryngeal nerve the rule is that the surgeon should stay close to

the adenoma surface during dissection and be exceedingly careful if diathermy is used. Patient who develop hypocalcaemia may need calcium supplements and may be vitamin D.[17-19]

Surgical indications in patients with PHPT may include symptomatic pHPT, when the serum calcium level is greater than 1 mg/dL above normal, regardless of whether objective symptoms are present or absent, objective evidence of renal involvement, including silent nephrolithiasis on renal imaging, nephrocalcinosis, hypercalciuria (24-hour urine calcium level >400 mg/dL) with increased stone risk, or impaired renal function (glomerular filtration rate <60 mL/min), osteoporosis, fragility fracture, or evidence of vertebral compression fracture on spine imaging, when pHPT is diagnosed at 50 years or younger regardless of whether objective or subjective features are present or absent, when the clinical or biochemical evidence is consistent with parathyroid cancer, for patients with neurocognitive and/or neuropsychiatric symptoms that are attributable to pHPT.[20]

To summarize, it can be stated that there is a correlation between the location of the parathyroid adenoma seen on the scintigraphic image and that seen with surgery. Secondly, all of the parathyroid adenomas were histopathologically confirmed. Therefore, I conclude that the dual-phased planar pinhole 99mTc-sestaMIBI scintigraphy in the preoperative localization of parathyroid adenoma in patients with primary hyperparathyroidism at the Universitas Academic Hospital, Bloemfontein is a useful preoperative investigative procedure in this group of patients.

LIMITATIONS OF THE INVESTIGATION

This study has some limitations such as; firstly, it was a retrospective study and hence it is a possibility that the various procedures done for each patient may not have been done in exactly similar circumstances, hence inter-patient variability may have existed in conducting the various procedures. Secondly, the size of the study group was small as some of the patients who would have been part of this study were excluded as some of their relevant data could not be found.

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