Minimally invasive, endoscopic assisted, parathyroidectomy (MIEAP) with intraoperative methylene blue (MB) identification

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Abstract Background: More than 85% of patients with primary hyperparathyroidism (PHPT) have a single adenoma. This fact when combined with the recent advances in preoperative imaging diagnostic modalities and intraoperative identification of the diseased gland has allowed the development of minimally invasive endoscopic assisted parathyroidectomy (MIEAP).

Objective: Treatment of patients with primary hyperparathyroidism due to a single gland disease, with minimally invasive endoscopic-assisted parathyroidectomy.

Subjects and methods: Nine patients (seven females and two males) with PHPT were proved to have a single-gland parathyroid adenoma after preoperative imaging techniques. They were scheduled for MIEAP, with intraoperative identification by MB.

Results: Surgical time ranged between 21 and 35 min through a small surgical wound and cure rate of 100% with no recorded complications.
1. Introduction

Bilateral neck exploration was the standard operation for primary hyperparathyroidism (PHPT). The goal of the procedure was to identify all four parathyroid glands and to remove all abnormal parathyroid tissues. A 70% cure rate was reported, but this approach was accomplished via a large incision with all its related morbidities and difficult second surgeries. More than 80% of parathyroid adenomas can be localized preoperatively. This idea together with the improvement in imaging techniques has made the application of minimal-access approaches to primary parathyroid disease a reality, also the combination of more than one imaging technique offers 95–98% accuracy. There are many reports of minimal incision parathyroidectomy with the intraoperative identification of the affected gland, with subsequent better and precise management of patients with less morbidity, less cost and much better cosmetic appearance than with ordinary wide approach.

Methylene blue (MB) has been used intraoperatively since 1971 to aid in gland identification as it selectively stains parathyroid tissues, thus facilitating surgery. The dye stains adenomas and hyperplastic glands a deep purple-blue color, while normal parathyroid tissue stains to a lesser extent or not at all. Up until recently, it has been considered a safe and cost-effective modality to use, whether by itself or as a complement to other preoperative imaging identification tools.

The aim of this work is to present the way for a minimally invasive, endoscopic-assisted parathyroidectomy (MIEAP) paved by preoperative imaging localization and intraoperative methylene blue (MB) identification.

2. Patients and methods

Nine patients with primary hyperparathyroidism (PHPT) due to single-gland parathyroid adenoma were treated by MIEAP. They were managed at Fakhry and AlRajhi Hospitals, AlKhobar, KSA, in the period between June 2005 and November 2010. The patients’ characteristics are summarized in Table 1. There were seven females and two males, with an age range from 42 to 53 years. Patients were evaluated by thorough history taking, clinical assessment and laboratory tests.

Ultrasoundography (US), CT, MRI and Technetium (Tc) m (sestamibi) scans were performed for 9, 6, 4 and 4 patients, respectively. Sestamibi scans were performed using the single agent wash-out technique and images were obtained at 10 and 90 min after isotope administration. Patients were scanned using a gamma camera. Parathyroid adenomas were localized preoperatively in all nine patients. Exclusion criteria for patient selection were: (1) non-localized adenomas, (2) previous neck surgery, (3) large goiters, (4) multiple endocrine neoplasia, (5) over weight, and (6) familial hypocalciuric hypercalcemia. Patients on drugs like acetylsalicylic acid, ibuprofen, high-dose vitamin E were instructed to stop medications 10 days before surgery to avoid perioperative bleeding. Patients taking antidepressant drugs were asked to stop medication 4 weeks before surgery.

A written informative consent was obtained from all patients participating in the study. The clinical research ethics committee of Fakhry and AlRajhi Hospitals approved the study and the related patients’ consent. On the day of surgery, all patients received preoperative intravenous Methylene blue (tetra-methylthionine chloride) infusion in 500 ml of 5% dextrose in a dose of 7.5 mg/kg body. The infusion was started 20 min before incision, and completed before exposure of the parathyroid gland. The anesthesiologist was alerted to the phenomenon of pseudocyanosis resulting from MB and the possibility of pseudohypoxia and encouraged to depend on pulse-oximetry.

In superior parathyroid adenomas, a 20 mm transverse incision was made in a skin crease directly over the localized parathyroid gland, along the medial border of the sternomastoid muscle. The sternomastoid muscle was mobilized laterally and the strap muscles medially to reveal the lateral margin of the thyroid gland. In inferior parathyroid adenomas, inci-

Table 1 Patients’ characteristics with various preoperative and intraoperative tools used to localize and identify parathyroid adenoma. Also, the maximum size of excised mass (in mm) and operative time (in min) are mentioned (F: female, M: male; RI: right inferior; Li: left inferior; RS: right superior; LS: left superior; MB: methylene blue).

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Site</th>
<th>Max. size (mm)</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
<th>Tc scan</th>
<th>MB</th>
<th>Time (min)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>44</td>
<td>LS</td>
<td>22</td>
<td>+ve</td>
<td>+ve</td>
<td>–</td>
<td>–</td>
<td>+ve</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>42</td>
<td>RI</td>
<td>14</td>
<td>–</td>
<td>+ve</td>
<td>+ve</td>
<td>–</td>
<td>+ve</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>42</td>
<td>RI</td>
<td>20</td>
<td>+ve</td>
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<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>50</td>
<td>LS</td>
<td>12</td>
<td>+ve</td>
<td>–</td>
<td>–</td>
<td>+ve</td>
<td>+ve</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>43</td>
<td>RS</td>
<td>23</td>
<td>+ve</td>
<td>+ve</td>
<td>–</td>
<td>–</td>
<td>+ve</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>53</td>
<td>Li</td>
<td>16</td>
<td>+ve</td>
<td>+ve</td>
<td>–</td>
<td>–</td>
<td>+ve</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>51</td>
<td>RI</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>43</td>
<td>RI</td>
<td>13</td>
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<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
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<tr>
<td>9</td>
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<td>44</td>
<td>LS</td>
<td>20</td>
<td>+ve</td>
<td>+ve</td>
<td>–</td>
<td>–</td>
<td>+ve</td>
<td>21</td>
</tr>
</tbody>
</table>

N.B.: (+ve) test done with positive detection, (–ve) test done with negative detection; (–) test not done.
sion was made 3 cm above the suprasternal notch and the strap muscles were separated in the midline. The 0° endoscope was used to help in dissection and identification of the blue-stained parathyroid adenoma (after methylene blue injection).

Complete hemostasis is insured, then wound is closed by subcuticular suturing, with no drains used. Immediate postoperative parathyroid hormone assay was requested. The specimen was sent for histopathology. All patients were considered for discharge the following morning. Calcium tablets were prescribed to be taken when needed and patients were given instructions on how to identify the symptoms of hypocalcemia. All patients were seen after 1, 3, 6 and 9 months postoperatively. The duration of operation (skin-to-skin time) was recorded, along with the length of hospital stay, complications and hormonal conversion rates.

Figure 1  (a) Coronal T2 weighted MRI showing hyperintense signal of left superior parathyroid adenoma (PTA, white arrows) and a nearby cervical lymph node (yellow arrow); th., thyroid gland; (B) axial T2 weighted MRI showing the hyperintense PTA (white arrows); (c and d) longitudinal and transverse cervical ultrasound showing the PTA (red arrows); (e) preoperative view of the patient showing the marking of the incision; (f and g) intraoperative endoscopic views showing the blue coloration of the PTA which is lying posterolateral to the thyroid gland (th) and anteromedial to the common carotid artery (cc); (h) postoperative view of the excised PTA and nearby lymph node (L.N.).

Figure 2  (a and b) Contrast enhanced coronal and axial CT showing a right inferior parathyroid adenoma (PTA, white arrows) lying above the brachiocephalic artery below the right hypoplastic thyroid lobe (th); (d) Technetium-99m sestamibi parathyroid imaging showing the PTA (black arrow); (e) preoperative view of the patient showing the marking of the incision; (e–g) intraoperative endoscopic views showing the blue coloration of the PTA which is lying lateral to the trachea (tr) below the right lobe of the thyroid gland with attached thymus gland, left lobe of the thyroid (th); (h) postoperative view of the excised PTA with attached fat (f), and thymus gland.
2.1. Statistical analysis

Descriptive statistics are presented as means, numbers and percentages.

3. Results

Nine patients with PHPT due to single-gland parathyroid adenomas constitute the main framework of this study. They were seven females and two males, aging 42–53 years (mean = 45.3). US was done for nine patients with a positive detection in six patients (66.7%) and negative detection in three patients (33.3%). CT was requested for six patients with 5 positive detections (83.3%), while the positive detections for MRI and sestamibi scans were (100%) in four patients (for each tool).

Preoperative imaging of all patients succeeded to localize the parathyroid adenoma (100%) using two modalities at least. Right inferior parathyroid adenoma (RI) (Fig. 2) was diagnosed in four patients (44.4%). Left superior parathyroid adenoma (LS), (Fig. 1) was diagnosed in three patients (33.3%), while the right superior (RS) gland adenoma was diagnosed in one patient (11.1%), the same value (11.1%) was recorded with left inferior (LI) adenoma.

All parathyroid adenomas were positively identified intraoperatively and stained by MB in all patients with no staining of the surrounding tissues e.g. thyroid gland, lymph nodes, and thymus gland (100% accuracy and 100% specificity). Skin-to-skin time ranged between 21 and 35 min (mean = 25.3). No postoperative complications, local or systemic, were detected. There were no postoperative vocal cord paralysis, or voice changes as confirmed by videolaryngoscopy, also no allergic or toxic reactions to MB were recorded. Two females complained of pain at the infusion site, that resolved by decreasing the rate of infusion. All specimens were proved pathologically to be parathyroid adenomas, ranging in size between 12 and 23 mm in maximum length (mean 17.1 mm). Hypercalcemia and parathyroid hormone were corrected in all patients and followed up for a minimum period of 9 months.

4. Discussion

For many years bilateral neck exploration with identification of four glands remained the gold standard in parathyroid surgery, and routine preoperative imaging for initial surgery was considered unnecessary and not cost effective. Time has changed, and undoubtedly it is the progress of imaging studies that has modified the surgical management of patients with hyperparathyroidism and helped the development of new surgical techniques.10

Recently, minimal-access parathyroidectomy is the current method of choice for 92% of members of the international association of endocrine surgeons.1,15,16 The concept of minimally invasive techniques is based on the fact that 85% of patients will have single-gland disease. The common thread of new minimally invasive techniques is that the approach is targeted on one specific parathyroid gland. In most cases the exploration of other glands is not performed.8,10 The morbidity associated with a standard four-gland parathyroid exploration could be minimized with a less invasive procedure while maintaining the same level of success at curing the disease.17

As the success of limited approaches largely depends on accurate preoperative localization, the surgeon is therefore highly dependent upon the quality of preoperative localization to make a judicious choice for a focused approach. Today, the development and the reported efficacy of noninvasive techniques have tempted many endocrinologists and many surgeons to order some of these new noninvasive techniques on patients undergoing first-time parathyroidectomy.10 Most institutions use preoperative imaging tools either a single agent or more commonly in combination.10,18-20

In this work, US was requested for the nine patients with positive detection in six (66.7%) of them. US is used as the first-line of parathyroid imaging for many reasons. It is easily and quickly performed, and well-tolerated by the patient. It does not require administration of contrast medium and does not emit radiation. It provides good anatomic information about masses in the neck, and when performed by expert radiologist, 95% of adenomas can be identified. In addition it is the least expensive preoperative localization technique. The sensitivity of US is operator, material and size dependent. The limit of detection is approximately 5 mm.18 US has been shown to have sensitivity and specificity of 70–85% and 90–95%, respectively.19

CT was ordered for six patients, with positive detection in five (83.3%) of them. It complements US in four patients and failed to detect the gland in one patient. CT imaging of parathyroid glands is relatively expensive, exposes the patient to radiation and requires the administration of contrast medium. It has a high rate of false-positive results, up to 50%.20 CT had been shown to have sensitivity of 67%.21 MRI and Technetium (Tc) scanning were the least tools used in this work, only in four patients, for each one, with positive detection in all of them (100%). MRI provides excellent anatomic details and is slightly more sensitive than CT. It does not require intravenous contrast. Nevertheless, MRI is expensive and patient compliance is sometimes limited by claustrophobia. Parathyroid adenoma typically has low signal intensity in T1-weighted imaging and high signal intensity in T2-weighted imaging.21 Sensitivity rates may reach up to 88%.22 Henry et al. 20017 stated that MRI is usually reserved as a second line test for localization in reoperative parathyroid surgery when US and sestamibi scans have failed to identify an abnormal parathyroid gland which is probably located in the mediastinum.

Cookley et al. first reported on the use of Technetium-99m methoxyisobutyl isonitrile (sestamibi) for parathyroid imaging.23 Sestamibi tends to be concentrated in parathyroid adenomas, but the exact mechanism remains debatable. High mitochondrial activity is considered to be the major component of sestamibi uptake by human parathyroid tissue in patients with primary hyperparathyroidism.1 The reported sensitivity is up to 90%.24,25 Wide differences in reported sensitivity exists.26

Authors in this work used MB in the preoperative period aiming for staining of the abnormal glands and hence intraoperative rapid and easy identification. MB is a cationic thiazine dye with a variety of uses including treatment of drug-induced methemoglobinemia, septic shock, treatment and prevention of ifosfamide-induced encephalopathy.27 In vitro experiments also show that intravenous doses of MB inhibit monoamine oxidase28 and may have direct hippocampal neuronal toxicity in rats.29 MB is primarily excreted in the urine after reduction by glucose-6 phosphate dehydrogenase (G6PD).30

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Since its description by Dudley in 1971, MB is used in some head and neck centers for parathyroid surgery due to the dye’s ability to preferentially stain the parathyroid glands. This enables greater surgical visualization and consequently easier resection. A dose up to 7.5 mg/kg is administered during the hour before surgery, as this is believed to provide optimal gland staining. Recent works had noted the development of transient neurologic side effects only in those patients who had been taking a drug that causes an increase in central serotonin transmission.

In its active site i.e. MB effectively functions as a MAOI. MAOIs are known to precipitate the development of serotonin toxicity, a rapidly worsening drug–drug interaction involving the accumulation of extremely high levels of serotonin, when coadministered with drugs that increase serotonin neurotransmission. Therefore, the combination of MB with a serotonergic drug results in a high risk of precipitating serotonin toxicity. Also Likier et al., 2008 observed that preoperative intravenous MB markedly decreased the anesthetic requirements and prolonged the time to awakening in patients undergoing parathyroidectomy.

In this work, all parathyroid adenomas were positively stained with MB, which was shown to be a useful diagnostic tool for patients of parathyroid diseases. The blue staining ensures easy visualization of abnormal parathyroid glands more easily. Until recently, it remains unelucidated why abnormal parathyroid glands are selectively stained with MB; however it was hypothesized by Takei et al., 1999 that both blood supply and retention are increased in the abnormal parathyroid glands compared to normal parathyroid glands or other tissues in the neck. Therefore MB would be easily absorbed into the abnormal parathyroid gland where it remains longer. In a study by Gordon et al., 1975 it was found that the staining affinity for the dye was directly related to the size of the gland. 87% of enlarged glands were stained, whereas only 25% of normal-sized glands were stained. When these characteristics were correlated with the histologic diagnosis, 100% of adenomas stained, 85% of hyperplastic glands stained and only 27% of normal glands stained. Also, Dudley considered that the intensity of staining with MB may be related to the number of oxyphil cells present in the gland such that the higher the number of oxyphil, the deeper the stain.

In our series, no complications associated with MB were recorded, either during early few hours or late postoperative follow up periods. This can be explained by the proper preoperative preparation and avoidance of those drugs that react and augment the toxic effects of MB.

In conclusion, patients with PHPT due to parathyroid adenomas could be managed by MIEAP in an easy and safe surgical technique and short operative time through a small and esthetic incision. These results are gained after proper preoperative preparation, imaging localization and intraoperative MB identification. Also, this technique shows less postoperative hypocalcemia and less postoperative scarring in the neck, allowing for safer reoperation if needed.

References
20. Takei H, Ino Y, Endo K, et al. The efficacy of technetium-99m-MIBI scan and intraoperative methylene blue staining for the


