

# Methylene blue infusion as intraoperative adjunct in parathyroid adenomas surgery

## *Detección intraoperatoria de adenomas paratiroides mediante infusión intravenosa de azul de metileno*

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### Key words:

Methylene blue, parathyroid, hyperparathyroidism, parathyroid adenoma.

### Palabras clave:

Azul de metileno, paratiroides, hiperparatiroidismo, adenoma paratiroideo.

### ABSTRACT

**Introduction:** The purpose of this study is to analyze the usefulness of methylene blue staining for intraoperative identification of parathyroid adenomas. **Methods:** A prospective longitudinal cohort study was performed. Operated patients with primary hyperparathyroidism were included. Methylene blue was used to dye and facilitate the identification of the pathological glands when there was discordance between preoperative information provided by the ultrasound and technetium <sup>99m</sup>Tc-MIBI. **Results:** Intraoperative infusion of blue methylene was used in 43 patients. In 37 cases adenoma was visualized in dark blue, clearly evident from surrounding tissues. In six patients (14%) adenoma was not detected due to mediastinal, paraesophageal or intrathyroidal location, they were found in the same operation but not stained due to the increase in surgical time. No false positive case was found. No neurotoxic side effects were recorded. All patients returned to normocalcemia. **Conclusions:** Blue methylene infusion is a helpful intraoperative adjunct for identifying parathyroid adenomas, it also provides additional information to the usual exploratory procedures, it is safe and easy to use.

### RESUMEN

**Introducción:** El propósito de este estudio es analizar la utilidad del azul de metileno como ayuda para la identificación intraoperatoria de adenomas paratiroides. **Métodos:** Estudio de cohorte, prospectivo y longitudinal. Se incluyeron pacientes intervenidos por hiperparatiroidismo primario. Se utilizó infusión intravenosa de azul de metileno intraoperatoria para teñir y facilitar la identificación de las glándulas patológicas cuando hubo discordancia entre la información preoperatoria aportada por la ecografía y la gammagrafía con tecnecio sestamibi (<sup>99m</sup>Tc-MIBI). **Resultados:** Se utilizó la infusión de azul de metileno en 43 pacientes. En 37 casos (86%) permitió visualizar el adenoma azulado que destacó claramente en los tejidos circundantes. Los seis pacientes en quienes no se detectó el adenoma (14%) se encontraban en posición mediastínica, paraesofágica o intratiroidea y no se visualizaron teñidos tras una larga disección y prolongación del tiempo quirúrgico. No se detectó ningún caso falso positivo. No se registraron efectos adversos graves o neurotoxicidad. Todos los pacientes volvieron a normocalcemia. **Conclusiones:** La infusión de azul de metileno es una técnica útil de ayuda intraoperatoria para la identificación de adenomas de paratiroides y complementa la información proporcionada por otras técnicas exploratorias habituales, además es segura y fácil de aplicar.

## INTRODUCTION

Surgery is the only potentially curative treatment of primary hyperparathyroidism. Detection of parathyroid adenomas is essential to obtain satisfactory results, a challenge to the surgeon on facing each case. Several factors make identification of abnormal parathyroid glands difficult, including their size, location, the presence of concomitant thyroid disease

or ectopic glands and the possibility of multiglandular involvement.<sup>1</sup>

There are adjunct diagnostic measures to locate the diseased gland preoperatively, such as ultrasound, neck computed tomography, magnetic resonance imaging, and technetium sestamibi (<sup>99m</sup>Tc-MIBI) scintigraphy.<sup>2</sup> The latter has become the diagnostic gold standard in many centers.<sup>3-5</sup> There are also intraoperative resources, such as parathyroid hormone (PTH)

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serial measurements in peripheral blood and intraoperative biopsy for anatomopathological confirmation.<sup>6</sup> The sensitivity and specificity of all these tests are variable. In Spain and worldwide, studies have been published on the usefulness of sestamibi scan, reporting an overall sensitivity of 89.46% and a variability of 75 to 92.5% when compared with ultrasound; the post-resection Miami criteria have established a sensitivity of 98% for the serial intraoperative PTH measurement.<sup>3-6</sup>

In 1971, Dudley proposed the infusion of methylene blue during surgery as a complementary method to locate parathyroid adenomas.<sup>7</sup> This technique has been reproduced by other surgeons for decades with promising results, but although it is a simple and inexpensive technique, its use has not become commonplace.<sup>8-12</sup> Perhaps this has resulted from evidence that methylene blue infusion may be associated to a certain neurotoxicity, and we believe this has given it an undeserved bad reputation, so there is no consensus on its use.<sup>13-21</sup>

The aim of this study was to analyze the usefulness of methylene blue in the intraoperative identification of parathyroid adenomas, as a complementary test during primary hyperparathyroidism surgery.

## METHODS

A prospective cohort study was conducted that included all patients treated surgically for primary hyperparathyroidism between January 2012 and January 2016, in the Department of General Surgery at the *Hospital Universitario Príncipe de Asturias* in Alcalá de Henares, Madrid, Spain. The operations were performed by general surgeons from the endocrine surgery division. Biochemical diagnosis was based on serum calcium and PTH determinations. Patients with a history of multiple endocrine neoplasia or familial hyperparathyroidism were not included. The study was approved by the hospital's endocrinology committee and registered under the number DAL-BEV-2012-01. All patients signed an informed consent form on the possible intraoperative use of methylene blue.

Location of pathological glands was previously defined in a protocol that included

<sup>99m</sup>Tc-MIBI scintigraphy and preoperative neck ultrasound. The ultrasounds were obtained on the day of surgery, immediately before the patient entered the operating room. The skin was marked at the point where the suspicious parathyroid was detected by ultrasound. All ultrasounds were performed by the same radiologist. Besides, serial blood PTH determinations and anatomopathological study of the specimen removed were carried out during surgery. PTH was measured by obtaining three blood samples: the first one, at the beginning of the cervicotomy; the second, upon identification of the adenoma; and the third, 10 minutes after removal. All tests were performed on all the patients included in the study.

Additionally, methylene blue infusion was selectively used. This test was applied when the information obtained by ultrasound and preoperative <sup>99m</sup>Tc-MIBI scan was inconclusive or inconsistent. Intraoperative methylene blue was also used when identification of the parathyroid glands was troublesome in spite of the preoperative information. Methylene blue infusion was not used in patients with the risk of potential neurotoxicity due to the regular use of serotonin reuptake inhibitors (SSRI).

In Spain, methylene blue is available commercially as 1% 10 mg/ml ampules. For the study, we used a dose of 5 mg per kg of weight diluted in 250-500 ml saline solution. This solution was administered intravenously as a rapid bolus over 10 minutes once the cervicotomy had begun. During the infusion, patients were continuously monitored and the anesthesiologist was warned about possible side effects, such as pseudoacidosis and pseudohypoxia registered by pulse oximetry. The degree of staining of the adenoma after administration of the dye was evaluated. It was described as null when the pathologic parathyroid maintained its usual color, moderate if the adenoma stained slightly blue, and intense when the adenoma turned a blackish blue color and clearly contrasted with the adjacent tissues.

Descriptive analysis of the quantitative data was performed using measures of central tendency and dispersion, according to normality criteria. Mean values were used for continuous

variables and percentages for categorical variables. Statistical analysis was performed with SPSS vs 22.

## RESULTS

During the study period, 103 patients were operated on, 79 (76.7%) females and 24 (23.3%) males, with a mean age of 55 years ( $\pm$  12.6 years). A selective cervical approach was used in 40 cases (38.8%) and bilateral neck exploration in 63 cases (61.2%). In 95 cases (92.2%), the adenoma was single, and in eight (7.8%), double adenomas were found.

Intravenous infusion of methylene blue was used in 43 patients (41.7%). This technique was not applied in 60 patients, i.e., in 14 because of potential neurotoxicity due to the regular use of SSRI, and in 46 cases because the adenoma's location had been clearly identified with the other preoperative tests.

Out of the former 43 patients, preoperative ultrasound correctly identified the adenoma's location by quadrant in 40 cases (93%), and  $^{99m}\text{Tc}$ -MIBI scintigraphy correctly located the quadrant where the adenoma was eventually found in 25 patients (58%). In no patient were these two tests simultaneously negative.

In the group of patients in which methylene blue was infused, a selective cervical approach was used in 18 patients (41.9%), and bilateral neck exploration was performed in 25 (58.1%). The mean preoperative serum calcium concentration was 11.56 mg/dl (range: 10.2-16 mg/dl). The mean serum PTH was 153 pg/ml (range: 52-574 pg/ml). PTH was within normal limits in only two patients, but they had decreased vitamin D levels, elevated serum calcium, and hypercalciuria, besides imaging results consistent with a parathyroid adenoma, so the multidisciplinary committee agreed on the removal of the adenoma. The vitamin D level was 22.4 ng/ml (range 14.2-27.5 ng/ml) and urinary calcium was 745.44 mg/day (range 202-1,292 mg/day).

The methylene blue infusion allowed the visualization of the adenoma in 37 patients (86%). In six patients (14%), the blue tinge of the adenoma was not evident after the dye infusion, due to a protracted dissection and an overlong surgical time searching for it, an

explanation that we deem relevant. In three of these cases, the adenoma was finally found in the mediastinum, in two patients it was in a low paraesophageal position, and in one case, it was an intrathyroid adenoma.

Single adenomas were identified in 37 cases (86.1%) and double adenomas in six patients (13.9%). The most frequent location was the right inferior quadrant, in 16 cases (37%). In 29 cases (67.4%), the adenoma stained deeply. The pathological gland was identified as a rounded oval shape, intensely purplish blue or blackish in color, that clearly contrasted with thyroid tissue or the surrounding connective tissues (*Figure 1*). In another eight cases (18.6%), staining of the adenoma was moderate, of a less intense blue. In the six cases with a double adenoma, both glands were visualized as similarly stained.

With this series, we have proven that intravenous infusion of methylene blue during surgery is quite useful to identify parathyroid adenomas intraoperatively. In 37 out of 43 patients (86%), the adenoma was stained by the dye, which made its visual identification easier. The other six cases, located extra-anatomically, were not stained when found. All the adenomas identified in their regular location (37 cases), and without an extended dissection time, were "hypercolored" by the blue dye (100%). It is worth noting that, in the six patients with double adenomas, both pathological glands were found equally stained. Considering the location by quadrant according to the preoperative tests, we should point out that methylene blue made the adenoma visible in 11 of 18 patients (61%) in whom  $^{99m}\text{Tc}$ -MIBI scintigraphy yielded an incorrect result, and in the three cases (100%) in which the information provided by preoperative ultrasound was not positive either.

No false-positive cases were found. All adenomas were located in a single surgical stage.

No severe adverse effects that could be attributed to methylene blue were seen, such as neurotoxicity. In all patients, a decrease in capillary oximetry was observed (mean oxygen saturation, 90%) at the time when methylene blue was administered, although it did not reflect a true decrease in blood  $\text{O}_2$  levels (pseudohypoxia) and it had no effect during



**Figure 1:** The pathological gland was identified as a rounded oval shape, intensely purplish blue or blackish in color, that clearly contrasted with thyroid tissue and the surrounding connective tissues.

surgery or after it. The urine transiently became a bluish color due to the dye's clearance. After removal of the adenomas, PTH decreased at least 50% in the obtained samples in all cases, fulfilling the Miami criteria for post-resection cure. The mean plasma PTH level after adenoma removal was 22.45 pg/ml. Intraoperative biopsy of the removed specimens revealed hyperplasia of the parathyroid tissue in all cases (100%). During the postoperative one-year follow-up, all patients maintained normal plasma calcium and PTH concentrations, with a mean PTH at one year of 32.50 pg/ml, calcium level of 9.8 mg/dl and no evidence of disease recurrence throughout the year.

## DISCUSSION

Surgery for primary hyperparathyroidism may be technically difficult, even for experienced surgeons. During the past decades, several tests have been developed to locate the pathological parathyroid glands and thus make their intraoperative identification easier.

Methylene blue belongs to a class of dyes known as thiazines, that includes toluidine blue, Azure A, B and C, and thionine.<sup>22</sup> All tissues uptake this dye, but the characteristically high metabolism of parathyroid adenoma cells leads to its rapid and intense capture, so the coloration of the adenoma stands out in

relation to the surrounding tissues, including the thyroid gland.

Since Dudley's initial description in 1981, several series have been published supporting the use of methylene blue infusions in surgery of the parathyroid glands. Kuriloff and Sanborn published a retrospective series of 35 patients who underwent bilateral neck exploration.<sup>22</sup> The infusion of methylene blue facilitated the identification of the abnormal parathyroid tissue in 97% of patients. According to these authors, the technique is safe, easily available, and affordable; it facilitates the identification of parathyroid adenomas and helps distinguish normal glands from hyperplastic ones.

Patel et al. published a review of 39 studies in which the authors used intravenous methylene blue during parathyroid surgery. Data collected highlighted the ability of methylene blue to stain pathological parathyroid glands, since the staining rates were close to 100%. Twenty-five patients developed severe side effects, i.e., transient postoperative neurotoxicity, pain at the infusion site, and nausea, all occurring in individuals that routinely used serotonergic medication. One death due to neurotoxicity was reported, but the patient also had severe cardiomyopathy that could have contributed to this outcome. There were no adverse events in patients that did not take SSRI. The data analyzed underscored the usefulness of methylene blue infusion as an intraoperative identification tool.<sup>17</sup>



When comparing our study with the main ones described in the literature and others previously cited, we again confirmed the ability of methylene blue to stain pathological parathyroid glands, with identification values of 100% in cases in which the adenoma was located in the regular position and dissection periods were not prolonged; furthermore, if we analyze individually the failures of each technique for surgical location, we consider that the infusion of methylene blue provided an added benefit, making it possible to identify 100% of cases in which ultrasound failed and 61% of cases in which  $^{99m}\text{Tc}$ -MIBI scintigraphy was wrong.

In this study, we analyzed the usefulness of infusing methylene blue as an intraoperative aid in the visualization of parathyroid adenomas. We did not intend to compare its performance with that of other diagnostic tests, much less to replace them. Methylene blue infusion was used as an adjunct in cases in which the information provided by the preoperative  $^{99m}\text{Tc}$ -MIBI scintiscan and ultrasound was inconsistent, but not with the aim of substituting any of the tests routinely used and internationally accepted.

At our center, cervical exploration is routinely performed in cases of primary hyperparathyroidism in which the preoperative tests disagree; the selective surgical approach, or localized focal parathyroidectomy, is reserved for cases in which the location coincides in both the preoperative scintigraphy and ultrasound.

The low sensitivity of  $^{99m}\text{Tc}$ -MIBI scintigraphy is striking in terms of locating the adenoma by quadrant, since it was only accurately located in 58% of cases, a very inferior rate compared to that described in other publications.<sup>23-25</sup> We consider this was due to failures in result interpretation on the laterality and location by quadrant. One must take into account that the group of patients studied is not a general series but a very select group; besides, the scan results were retrospectively interpreted, and the images were obtained in three different radiology units.

Preoperative ultrasound did yield a high percentage of accurate diagnoses, since it was performed by the same expert radiologist in all cases, and correctly located the adenoma in 93% of patients; in the remaining patients, there

was disagreement on the part of the radiologist as to the location (superior or inferior), but not the laterality (left or right).

Several reviews have found out that the factor limiting the widespread use of this technique has been fear of the development of adverse effects, particularly the potential for neurotoxicity. It is currently known that methylene blue has similar properties to those of monoamine oxidase inhibitors (MAOI). When coadministered with drugs that increase serotonin neurotransmission, such as SSRI, adverse effects may develop, such as metabolic encephalopathy due to serotonin accumulation. It is therefore recommended to avoid using methylene blue in patients treated with that kind of drugs and, in any case, to limit the dose to 10 mg/kg.<sup>13-21</sup> At this dose, no significant adverse effects have been reported. In our study, a dose of 5 mg per kg of body weight diluted in 250 ml saline solution was used, and we observed no evidence of toxicity or adverse effects.

It is known that, during the period in which the dye is infused, a bluish hue is seen in patients (pseudocyanosis) that lasts for a few minutes until the dye is cleared from the body and has no consequences. Also, for this reason, the measured value of oximetry based on capillary transillumination methods (pulse oximetry) is temporarily invalidated, since it does not reflect actual hypoxia.

## CONCLUSIONS

Intravenous infusion of methylene blue is a useful technique for the intraoperative identification of parathyroid adenomas, and complements the information provided by other routine diagnostic techniques, without intending to replace them.

It is a safe and easily applied technique; after using the adjusted dose in several patients, no complications were observed nor was there evidence of neurotoxicity.

Our recommendation is to use methylene blue as an intraoperative adjunct in cases in which routine preoperative diagnostic tests are inconsistent, complying with the required safety measures and individualizing to each patient, since the infusion may

provide an additional benefit when identifying pathological glands.

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