

# Role of Methylene Blue Infusion in Per-Operative Localization of Parathyroid Glands

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## Introduction

Hyperparathyroidism (HPT) is a disease of diverse clinical presentation. Adenoma, hyperplasia and carcinoma of parathyroid glands form the common basis for the etiology of primary hyperparathyroidism. The clinical presentations of Primary HPT are innumerable with a wide variety of available diagnostic and localization techniques. However, as far as the treatment is concerned, surgery is at present the only potentially permanent solution. A variety of localization techniques have been used for preoperative and

per-operative localization of the parathyroid glands with variable sensitivity and specificity.<sup>1</sup>

The initial exploration for primary HPT is successful in 90 - 97 % of cases in which the abnormal glands have not been localized prior to surgery, and the surgeon is "experienced" in parathyroid gland surgery.<sup>2-4</sup> In the third world clinical setup, where referral system and subspecialty centers are not in vogue at the moment, preoperative localization of Parathyroid glands is required. Intraoperative infusion of methylnine chloride tetramethylthionine

chloride (methylene blue) for localization the Parathyroid glands is a less costly method as compared to newer preoperative localization techniques, and perhaps more practically effective for third world countries. The introduction of methylene blue for rapid intraoperative identification of the parathyroid glands is credited to Dudley<sup>5</sup> and later augmented by others.<sup>6</sup>

Five cases of primary HPT are reported, each with a different clinical presentation and cause of the disease. The experience of intraoperative localization of the parathyroid glands using methylene blue infusion, a long forgotten method, is also revisited in this article.

**Table 1. Methylene blue Infusion Scoring Scale (MISS) for the Change in color of parathyroid gland.**

Score	Interpretation
0	No uptake, no or very little difference in color, no blue tinge
1	Little uptake, mild difference in color, very light blue tinge, only obvious on close observation
2	Good uptake, moderate difference in color, blue tinge visible without difficulty
3	Excellent uptake, gland turned deep blue to purple in color

The aim of this prospective study was to evaluate the use and safety of methylene blue infusion in the intraoperative localization of abnormal parathyroid glands and whether it can compensate for the non-availability of expensive investigation tools for preoperative localization and relative lack of experience in parathyroid surgery in a developing country.

## Patients, Methods and Results

All patients with biochemically proven primary HPT, undergoing surgery from September 1998 to August 2001, were included in the study. Demographic data, mode of admission, history, examination findings, and provisional diagnoses were recorded. Sestamibi scan was performed on each patient prior to neck exploration. All the patients included in the study underwent bilateral neck exploration. Surgery was conducted by the most senior surgeon in the department of general surgery. Transfusion of 20 milliliters of sterile 2% solution of methylene blue in 500 ml of 0.9% saline was started 15 to 30 minutes prior to induction and continued till the time of incision. During the infusion all patients were monitored (continuous electrocardiogram and vital signs). On exploration the parathyroid glands to be excised were examined by the primary author for change in color compared to the surrounding tissue, which does not take-up methylene blue. The change in color was rated on a Methylene blue Infusion Scoring Scale (MISS) (Table 1). Changes in the region of 2 and 3, according to the scale, were considered significantly helpful in localizing the gland. All identified and excised glands were sent for frozen

**Table 2. Results.**

S.No	Age (years)	Sex	Presentation	Scan result	MISS score	Diagnosis
1	22	F	Weakness, low grade fever for 2 months	Hyperactive left upper PTH gland	3	PTH adenoma
2	58	F	Acute pancreatitis with drowsiness and confusion for 24 hours	Hyperactive right upper PTH gland	3	PTH adenoma
3	73	F	Joint pains for 12 months	Hyperactive left lower PTH gland	2	PTH adenoma
4	16	M	Generalized bone pain, loss of visual acuity, diagnosed case of MEN I syndrome	All four hyper-functioning glands	3,2,2,1	Hyperplasia with adenoma of one gland
5	28	M	Recurrent fractures, UTI, weight loss and depression for 4 months	Hyperactive and enlarged right upper PTH gland	3	PTH adenocarcinoma

F = Female, M = Male, PTH = Parathyroid

section (for confirmation) and later for formal histopathological examination.

At the end of the study period, variables in all the cases were studied. The findings of the Sestamibi scan and per-operative localization of the parathyroid glands by methylene blue were compared.

Surgery was performed in 5 patients (2 males, 3 females) surgery for primary HPT (Table 2). Mean age was 38.4 years. Each patient had a different clinical presentation. Sestamibi scan done in all five patients showed a single hyperfunctioning gland in 3 of them. All were reported as an adenoma after histopathological examination. A young boy with Multiple Endocrine Neoplasia Syndrome type 1 (MEN-1) showed hyperfunction of all four glands on Sestamibi scan while the histopathology report revealed adenoma in one of the gland with hyperplasia of the other three glands. Sestamibi scan of a patient with recurrent fractures revealed a single enlarged hyperactive gland, which was an adenocarcinoma on histological examination.

A total of eight glands were removed from five patients. Four out of eight showed an excellent uptake of Methylene-blue (MISS - 3), three of them showed a good uptake (MISS - 2), while one gland did not show any significant uptake (MISS-1, this was the last of the explored glands in the patient with MEN syndrome).

None of our patients showed untoward effects (arrhythmias, change in pulse rate or blood pressure) during the infusion of methylene blue. Although the colour of urine of all patients turned blue and had a tinge of blue for some days.

## Discussion

Ever since it has been possible to measure serum calcium, the annual incidence of primary HPT has risen and the proportion of cases with asymptomatic disease has also increased.<sup>7</sup> In developed countries, almost all parathyroid surgery is performed in centers or departments of Endocrine surgery. In developing countries where a referral system is not established, surgeons with experience (but not necessarily in parathyroid surgery) usually undertake the procedure. In such situations preoperative localization has significant value.

Primary HPT continues to be a disease of middle or late life, particularly in women, and frequently exists in a mild form.<sup>8</sup> These facts and the variety of presenting clinical features of HPT are quite evident even in our small patient group. In 1990 the National Institute of Health (NIH) in the UK concluded that preoperative localisation of the parathyroid glands is unnecessary for primary exploration.<sup>9</sup> Bilateral neck exploration performed by an

"experienced parathyroid surgeon" is curative in excess of 95% of cases.<sup>2,3,4,10</sup> Although the debate of who is to be called an "experienced parathyroid surgeon" is unsettled, however, the fact that preoperative localization of parathyroid glands is needed in the developing countries is understandable.

Due to the small size, variable appearance and anatomical location, the intra-operative search for parathyroid glands is more often than not a source of frustration for the surgeon and can significantly prolong the operating time. Per-operative staining of parathyroid glands by intravenous infusion of methylene blue has been shown to overcome these problems.<sup>11</sup> In our series of eight parathyroid glands, seven showed excellent / good uptake of methylene blue. This uptake was helpful in the localization of the glands. It also corresponded with the abnormal glands on the Sestamibi scan. Dudley, in 1971, introduced this use of methylene blue and considered it reasonable and safe.<sup>5</sup> In 1975 Gordon and co-workers advocated the use of Methylene blue for this purpose.<sup>12</sup> Cox and colleagues, in 1979, reported the application and efficacy of this technique.<sup>11</sup> In 1985 Bland and associates reviewed the technique and reported a significant reduction in operating time due to the ease in locating the glands.<sup>13</sup>

During the last two decades the role of methylene blue faded away giving way to newer techniques (conventional and endoscopic Ultrasound, Computed tomography scan, Magnetic resonance imaging, Radio-nuclide scans and preoperative use of gamma-probe).<sup>1,14-16</sup> Technetium-Sestamibi scan is considered to be the preoperative localization technique of choice at the moment. These investigations are now indicated for recurrent HPT which entails technically difficult surgery even for "experienced parathyroid surgeons".<sup>1</sup>

In developing countries it is not possible to use such a variety of investigative tools in all cases of primary HPT (because of expense or availability), nor are "experienced parathyroid surgeons" easily available. Therefore, the role of methylene blue infusion in per-operative localization of parathyroid glands should be reconsidered to achieve the benefit of reduction in operating time, ease of identification of glands intraoperatively and facilitating the cost-effective management of primary HPT.

## Conclusion

The experience with methylene blue infusion in per-operative localization of parathyroid glands, supported by world literature, show that intraoperative methylene blue infusion is an effective and safe method for localization of abnormal parathyroid glands and can compensate for the non-availability of expensive pre-operative investigations and relative lack of experienced parathyroid surgeons in the developing countries.

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