



Intra-operative Parathyroid localization in Primary Hyperparathyroidism in a resource constrained part of India- a case report and a review of literature

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Background

In the Indian subcontinent, the concept of endocrine surgery is gaining its popularity. Every year highly qualified endocrine surgeons are passing out from their reputed institutes. Many of them operate parathyroid tumors in primary hyperparathyroidism (PHPT) in the areas with limited facilities like the intra-operative nuclear scanning and intra-op PTH estimation. Should the surgeons stop practicing parathyroid surgery in the absence of such high-end investigations or they can make use of some commonly available adjuncts like methylene blue to localize the abnormal parathyroid glands intra-operatively especially in complicated cases? The role of methylene blue in various localization studies like sentinel lymph nodes biopsies are well established, but its role in the parathyroid localization is still debatable. With the help of a case report, we reviewed the literature to find out the safety and efficacy of the methylene blue in the intra-operative localization of abnormal parathyroid glands and whether it can substitute the not so readily available expensive investigations.

Case Report

A 44 years old male, sub-inspector by occupation presented with the complaints of recurrent nephrolithiasis, frequent graveluria, and recurrent urinary infections for 18 years. Other than that he did not exhibit any features of overt metabolic bone disease, syndromic features, gatro-intestinal symptoms, or body weakness. He had a non-contributory family history, but had compromised renal functions on Renal Dynamic Scan and underwent repeated nephrolithotomies both open and endoscopic for

renal stones. He was under work up in the reputed institute of the country, where he was diagnosed as a case of Primary Hyperparathyroidism biochemically, but the lesion was not localized even with repeated attempts of ultrasound, MIBI scan, and CECT Neck. Since he only had the reports and not the images, we repeated the investigations which further confirmed the diagnosis of primary hyperparathyroidism with metabolic bone disease and nephrocalcinosis. Table 1. In the MIBI scan, though, the endocrine surgeon could appreciate the subtle lesion in delayed images in the right inferior region; the nuclear medicine physicist reported it as negative for any abnormal uptake. Keeping in mind the importance of imaging, the endocrine surgeon and the experienced radiologist together did the USG neck and subsequent CECT neck and could appreciate the subtle lesion in the right inferior region, but the lesion was too small to be sure of parathyroid tumor. (Figure 1.).

Owing to the inconclusive pre-operative localization studies, he was planned for bilateral neck exploration under general anesthesia. Though we had the facility of parathyroid scans we lacked facilities of intra-op nuclear scanning, intra-operative frozen section biopsies or intra-operative parathyroid measurement. After proper consent, we took the patient for bilateral neck exploration with intra-operative methylene blue infusion technique to aid our detection of abnormal parathyroid.

Since the team was new to this procedure, to avoid the risk of any mishap, after a test dose, we infused the methylene blue solution @ 2mg/ kg body weight in 100 ml of normal saline, (despite the recommended 5-7.5 mg/kg of body weight), started 20 to 30 minutes before induction and completing

just before the incision. During exploration, we found a clear bluish discoloration of the right inferior parathyroid gland. The gland was enlarged 1x 0.5 cm, elongated, and encapsulated. All the other three glands were identified and were seemingly normal and unstained. The thyroid was also slightly bluish in colour. The right inferior parathyroid gland was excised and biopsies were taken from the other three parathyroid glands (Figure 2). Since our institute did not have the facility for frozen section, we sent the tissue to definitive histopathological examination only. Postoperatively, the patient developed mild hypocalcaemia which was managed with oral calcium and vitamin supplements. The histopathology reported as parathyroid adenoma with normal other three parathyroids. Before his transfer to another city, he came for follow ups for next 2 years during which time his nephrocalcinosis decreased, with no new stone formation. His frequency of urinary infection and fever decreased with improvement in renal functions. His iPTH dropped to 26 pg/ml (14-72 pg/ml) with serum calcium 8.9 mg/dl (8.5-10.5 mg/dl).

Investigation	Value	Reference Range
iPTH	235.8 pg/ml	15- 65
S Calcium	11.2 mg/dl	8-10
I Phosphorous	2.6 mg/dl	2.5- 4.5
25 OH vitamin D	13.2 ng/ ml	20-100
Uric acid	8.4 mg/dl	2-7.4
Alkaline phosphate	479 mg/dl	80-240
TSH	4.51	0.3-4.2
Prolactin	8.32 ng/ml	6- 29.9
BMD	T SCORE	Z SCORE
WRIST	-2.9	-2.6
HIP	-1.6	-1.1
SPINE	-1.9	-1.8

Discussion

The awareness regarding the parathyroid surgery is on the rise. The trained endocrine surgeons are passing out every year from their reputed institutes to work at new and remote places creating awareness about these disorders and providing surgical facilities to the needy patients. The endocrine surgery being at its initial phases in those regions, many times the high-end investigations are not available (1, 2, 3, 4, 5, 6). Many surgeons with an interest in parathyroid surgery are thus stuck to decide whether or not to operate a patient with inconclusive parathyroid localization. But with an optimistic vision, if we look

back at the history of parathyroid surgery, there was a time when “an experienced parathyroid surgeon” was considered the “best to localize the parathyroid tumors”. In this case, we tried to prove this dictum with the help of a commonly available and cheap dye known as methylene blue.

About methylene blue

Methylene blue, also known as methylthionium chloride, was first developed by Heinrich Cairo in 1876 (7). It is the first fully synthetic drug used in medicine (8, 9). Since its first use in medicine as a treatment for malaria in 19th century, it has been used in a variety of clinical conditions like methemoglobinemia (10), plaque psoriasis (11) urinary tract infection (12), cyanide poisoning (13), ifosfamide poisoning (14), septic shock and anaphylaxis (15) and as a dye in cancer surgeries (16), sentinel lymph nodes biopsies (17), sinus and fistula surgeries (18) and to monitor the compliance with the psychiatric medicines. (19).

Its dry form exists as dark green crystal and in solution, it turns into the deep blue. It can be given both orally and intravenously and for external use also. It is excreted by kidney, liver which results in the bluish discoloration of the urine and stools for several days after administration. Doses over 7.5 mg/kg may result in gastrointestinal symptoms. It shares the structural similarity with monoamine oxidase inhibitors and therefore may precipitate the signs and symptoms of serotonin-induced neurotoxicity with drugs that increase the levels of central serotonin levels like the SSRIs. (20)

Methylene blue in parathyroid surgery

In 1971, Dudley first advocated the use of methylene blue infusion in parathyroid surgery In his study of 17 patients, he found 41 abnormal glands and had a 100 percent cure rate. He used a calculated dose of 5 mg/kg body weight in 500 ml of 5% dextrose and 1/5 normal saline and given intravenously for one hour before surgery. In his experience, the color of the abnormal parathyroids was stained dark blue to purple whereas the normal parathyroids, thyroids, and muscles stained dusky slate blue. The intensity of staining increases up to one hour after infusion lasts for 20 minutes before diminishing over the next 2-3 hours. (21)

DJ Sherlock et al, in his study on 40 patients with hyperparathyroidism found almost 100% detection rate of pathological glands which are characteristically more intensely stained than the normal parathyroid

glands. The staining was consistent. The glands were visualized through various tissue layers, which aided in surgical dissection. (22)

MH Thabet et al. published his results of intra-operative use of methylene blue infusion @ 7.5 mg/kg, as an adjunct to Minimally Invasive, Endoscopic Assisted Parathyroidectomy (MIEAP). In his study on 9 patients, the adenoma detection rate was 100% with no staining of normal parathyroid glands with the additional advantage of decreased surgical time (23)

MS Shamim, in his study, tried to score the uptake of the methylene blue by the parathyroid glands. Score 0- no uptake or no or very little difference in color, no blue tinge; Score 1- Little uptake, a mild difference in color, very light blue tinge, only obvious on close observation; Score 2 - good uptake, the moderate difference in color, blue tinge, visible without difficulty; Score 3 -Excellent uptake, gland turned deep blue to purple color. 8 glands were removed from the 5 patients, one of them had MEN syndrome. Four out of eight glands showed excellent uptake, three showed good uptake and one showed no uptake (Patient with MEN syndrome). (24)

Bewick J in his study found a sensitivity of 78.9% with methylene blue which was in line with the USG (79%) and parathyroid scintigraphy (88%). The study recommended methylene blue as an adjunct to these measures by complementing and confirming the finding especially in multiglandular and ectopic diseases where the sensitivity rates are quite lower. It helps in distinguishing the blue stained parathyroid gland from the other tissues like lymph nodes. (20)

None of the studies faced any problem associated with the administration of the dye. The patient's acceptability was excellent except. The side-effects are usually mild and self-limiting, like bluish discoloration of urine and other body fluids, which is very well tolerated if the patient is counseled pre-operatively. It demonstrates the synergistic effects of anesthetic drugs and can prolong the arousal time; therefore, they must be used judiciously. Overdosage of anesthetic drugs may lead to methylene blue encephalopathy; therefore, patients with delayed arousal must have brain monitoring. Though neurotoxicity is a dreaded complication, it is very rare and almost all these neurotoxicity are reported in patients receiving anti-depressants especially SSRI (Selective Serotonin Re-uptake Inhibitors). This can be avoided either by not giving methylene blue to those taking SSRI or switching the patient to other safe alternatives in consultation with the physician.

Haciyani M et al, reviewed their results of the ultrasound guided methylene blue injection in the parathyroid tumors of the patients with re-operative recurrent hyper-parathyroidism. In their technique, they injected a 0.2 ml of the 1:5 diluted 1% methylene blue directly into the adenoma with a tuberculin syringe and before removing the syringe they instilled another 0.1 ml of the dye just under the skin to guide the incision. In their experience the blue dye was not scattered around and confused the anatomy (25). Though they reported this technique as useful, but pre-operative localization by means of staining the parathyroid glands can only be useful if the surgeon is sure of the particular lesion as parathyroid tumor only.

A very detailed review published by Patel et al showed methylene blue to be efficacious with a 100% staining rate of abnormal parathyroid glands. The methylene blue arm group had a 100% cure rate compared to the non-methylene blue arm. The untoward effects were high in the methylene blue group but the majorities were harmless like discoloration of urine and the serious side-effects were limited to those taking SSRIs. (26)

Table 2: - Summary of the methylene blue staining characteristics in parathyroid surgery.

S	Study type/ sample size	Dose	Timing of infusion	Staining of abnormal glands	FP/ FN	Differentiating features (if any)	Cure rates	Adverse drug reactions/ Complications
Bewick J (20)	Prospective/ 98cases	3.5 mg/kg BW in 500 ml of DNS	One hour prior to surgery	78.6%	FN - 15.5%; FP- X	X	X	Neurotoxicity- 0 Hypotension- 2 Wheezing – 1 Transient bradycardia- 1 Injection site pain – 2
Dudley (21)	Prospective/ 17 cases	5 mg/kg BW in 500 ml DNS	One hour prior to surgery	41 out of 68 parathyroid glands found Abnormal glands- dark blue to purple	X	Normal glands- dusky slate blue;Thyroid glands, thyroid cysts and strap muscles took light blue tinge	X	No troublesome side- effects
DJ Sherlock et al (22)	Prospective/ 40 cases 12 with secondary or tertiary HPT	5-7.5 mg/kg BW	One- two hours prior to surgery	All 4 glands were demonstrated in 38 patients. In 2 cases 3 glands were demonstrated	X	Normal glands stained less deep than pathological glands. Adenomas stain dark blue and hyperplastic stained light blue	39 out of 40 patients achieve eucalcemia. One patient had supernumerary ectopic gland requiring re- exploration	One case of nausea due to rapid infusion
MH Thabet et al. (23)	Prospective/ 9 cases with PHPT	7.5 mg/kg BW in 500 ml 5D.	Started 20 minutes before incision	All tumors stained (100% accuracy and 100% specificity)	0%	No staining of surrounding tissues, like thyroid, lymph nodes and thymus	100%	Injection site pain due to high flow
MS Shamim (24)	Prospective/ 5 cases	20 ml of 2% methylene blue in 500 ml NS	15-30 minutes prior to incision till incision	4/8 showed excellent uptake; 3/8— good uptake; 1/8—little uptake	X	X	X	Only transient discolouration of urine
Patel et al (26)	Systematic review/ 39 studies	5-7.5 mg/kg BW in 200 to 500 ml of infusion fluid	Majority completed infusion just before incision. Few gave boluses or Infusion after intubation	Overall median staining rate SGD and MGD was 100%	Median staining of - Normal glands – 59%; Lymph nodes- occasional; Thyroid - 14.4%	X	Overall median cure rate (SGD and MGD) for methylene blue arm was 100% and non- methylene blue arm was 98%	Common- pseudocyanosis, pseudohypoxia, temporary discoloration of urine, pain at infusion site, nausea; less common – neurotoxicity, esp in patients already on SSRIs

Conclusion

During the last few decades, the role of methylene blue is taken over by newer techniques. Its worth is under-estimated and its side-effects are over-hyped. In developing countries or areas with budding endocrine surgery, it is not possible to use these varieties of investigations due to lack of availability and cost. "The eyes don't see what the mind don't know" - An experienced parathyroid surgeon is a must for the parathyroid surgery, however the preferential staining of the abnormal parathyroid tissues with methylene blue can assist the surgeon especially in technically challenging cases in a resource constraint condition to decide the extent of the parathyroid excision. The world literature also supports the use of methylene blue infusion in an effective and safe method, which can compensate for the non-availability of expensive and versatile per-operative investigations. Additionally, it has the advantages of being cheap, readily available, requiring no additional equipment and with no serious side-effects except for those taking SSRIs, which can easily be avoided by taking the drug history. Therefore the use of methylene blue in the parathyroid surgery must be re-considered to achieve the cost-effective management of the primary hyperparathyroidism

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