

Subject Area: Oncology

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# Using methylene blue spray intraoperatively to perform safe thyroidectomy

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## Abstract

### Background

Recurrent laryngeal nerve (RLN) injury and hypoparathyroidism are serious complications following thyroidectomy. Minimizing these complications is important to avoid a destructive life-long handicap.

### Aim

Our goal was to decrease the incidence of intraoperative mishaps by spraying methylene blue dye on thyroid tissue and the tissues nearby.

### Patients and methods

This is a prospective study that included 90 patients who underwent primary thyroid surgery for various thyroid diseases, with total thyroidectomy done in all. The patients were divided into two groups: methylene blue group included 45 patients who underwent surgery using methylene blue technique, and conventional group included 45 patients who underwent surgery using the conventional technique. Spraying of 0.5 ml of methylene blue stain (normal saline) (2 : 8) following superior pole ligation was done. Thyroid tissue of a lobe and perilobar area were exposed to the methylene blue dye spraying, with identification and evaluation of the RLN and parathyroid tissues.

### Results

RLN and inferior thyroid artery stayed white in color in every case, but other tissues have been stained by blue color, with different times of fading out. Parathyroid glands stained for 3 min before fading out. Time for wash-out of thyroid gland was 15 min, whereas fading out time for other tissues, such as perithyroid tissues, tendinous, and lipid structures was ~25 min.

### Conclusion

This research aims to show the efficacy of methylene blue spraying as a safe procedure for identification of different important structures in close relation with the operative field such as RLN and parathyroid glands intraoperatively to do safe thyroidectomy.

**Keywords:** Intraoperative, methylene blue, safe, spray, thyroid

## INTRODUCTION

Following diabetes mellitus, disorders of thyroid endocrine gland are considered the second leading cause of endocrinal disorders [1].

Thyroidectomy is the surgical treatment of choice in thyroid neoplasm and most thyroid diseases [2,3].

Hypoparathyroidism and recurrent laryngeal nerve (RLN) injuries are serious complications following thyroidectomy [4].

Thyroidectomy complicated with hypocalcemia leads to patient discomfort, increase in postoperative morbidity, and prolonged hospital admission. Multiple factors are responsible for postoperative hypocalcemia such as extent of the surgery,

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iatrogenic hypoparathyroidism, how many of residual functioning glands, in addition to experience of the operator [5,6].

RLN injury is a destructive life-long handicap but still with low overall incidence. Identification of RLN by its anatomical site is still considered the safest way for reducing injury to it. Identification of the RLN in place has long been accepted as the safest way of decreasing possibility of nerve injury [7].

Identification of parathyroid glands by intravascular injection of toluidine blue staining was reported for the first time in animals by Klopper and Moe [8].

The parathyroid identification technique via intravenous infusion procedure by Dudley and colleagues was applied on 17 patients with complete histological confirmation, which was done for all cases.

The same procedure was applied on 59 patients by Elias and colleagues who underwent thyroid gland surgery (23 with malignancies).

Accurate localization of the glands has been amenable for 87%.

The aforementioned intravascular procedure verifies only parathyroid gland identification to prevent hypoparathyroidism and hypocalcemia [9–13].

There has been a search for another alternative staining dyestuff other than toluidine blue dye, as its general use has been held up for its many negative adverse effects [14].

Methylene blue stain was used to stain vagus nerve, facial nerve, and autonomic nerve fibers [15,16]. Sari *et al.* [17] used methylene blue spray intraoperatively to do safe thyroidectomy.

In this study, we assessed the application of methylene blue dye in total thyroidectomy for safe identification of parathyroid glands and RLN.

## PATIENTS AND METHODS

This study was performed on 90 patients who underwent primary thyroid surgery for various thyroid diseases, with total thyroidectomy done in all between June 2017 and July 2019. It was carried out in the Surgical Oncology Department, Al-Ahrar Zagazig Teaching Hospital, Egypt; in General Surgery Department, Banha Teaching Hospital, Egypt; and in General Surgery Department, Alsahel Teaching hospital, Egypt. Informed consent (written) was obtained from all patients.

### Study design

This study was a randomized controlled trial. The included 90 patients were divided into two groups: methylene blue group included 45 patients who underwent surgery using methylene blue technique, and conventional group included 45 patients who underwent surgery using the conventional technique. These patients with benign and malignant goiter disorders underwent total thyroidectomy in the Surgical Oncology Department, Al-Ahrar Zagazig Teaching Hospital, Egypt; in General Surgery

Department, Banha Teaching Hospital, Egypt; and in General Surgery Department, Alsahel Teaching hospital, Egypt.

Indications for surgical treatment were as follows:

Single nodular goiter (77), malignant nodule (five), primary toxic goiter (five), and secondary toxic goiter (three).

Exclusion criteria were as follows:

Recurrent surgery, cord dysfunction before surgery, giant goiter (narrow operative field), and retrosternal goiter.

Surgery was performed by well-experienced surgeons.

In each patient, indirect laryngoscopy was done before and after surgery to assess the condition of vocal cord motility. Postoperative calcium level less than 8 mg/dl was considered as a cutoff value for postoperative hypocalcemia, with clinical manifestation of temporary hypocalcemia also being reported. T3, T4, TSH, and ultrasound neck were done.

### Technique

For bilateral total thyroidectomy under general anesthesia, a standard Kocher incision was performed, followed by ligation of middle thyroid vein to facilitate thyroid lobe dissections.

Ligation and cutting of the superior pole were done. Here and at this step, there is no identification of the two important structures (parathyroid glands and RLN) (Fig. 1).

Before ligation of the inferior pole, medial deviation of thyroid lobe was done to spray 0.5 ml methylene blue (in sterile spray bottle) over the thyroid lobe and perilobar area.

With the following structures included in this area such as the parathyroid glands, inferior thyroid vessels (artery and veins), RLN, and perithyroidal muscles, and tendinous and lipoid structures, tissue identification and evaluation were done with special care for the most two important structures (RLN and parathyroid glands).

Parathyroid gland wash-out time was usually after 3 min, whereas for thyroid glands was after 15 min, and perithyroid after 25 min.

During surgery, and after careful dissection and identification of all parathyroid glands, especially their vascular pedicles. RLN was not stained (white color) (Fig. 2).

There was no need for autotransplantation into the sternocleidomastoid because there was no damaged parathyroid gland.

### Statistical analysis

Data were collected, then revised, coded, and supplied to the program of Statistical Package for Social Science (version 23; IBM Corp., Armonk, New York, USA). Qualitative variables were assembled as number and percentages, whereas quantitative variables when symmetrically distributed were presented as mean, ranges, and SDs. Moreover, comparison

between different groups with qualitative data has been done by using  $\chi^2$  test. However, comparison between every two independent groups with quantitative data has been done by using independent  $t$  test, whereas between every two paired reading in the same group, the comparison was done by using paired  $t$  test. The confidence interval was set at 95%, and the accepted error has been set to 5%. So, the level of significance of  $P$  value has been at the level of less than 0.05.

## RESULTS

This study included 90 patients who underwent total thyroidectomy. The patients have been divided into two groups: methylene blue group included 45 patients who underwent surgery using methylene blue technique, and conventional group included 45 patients who underwent surgery using the conventional technique.



Figure 1: Before methylene blue spraying.

Regarding patients' epidemiological characteristics as shown in Table 1, there has been no significant difference in the mean age of patients, with  $37.12 \pm 8.25$  and  $39.6 \pm 10.25$  years in methylene group and conventional group, respectively ( $P = 0.209$ ,  $t = 1.264$ ).

Patients' sex had no significant difference in this study. The methylene blue group included eight (17.8%) males and 37 (82.2%) females, whereas the conventional group included nine (20.0%) males and 36 (80.0%) females ( $P = 0.787$ ,  $t = 0.073$ ). The mean BMI of patients was  $31.35 \pm 5.74$  kg/m<sup>2</sup> in methylene blue group, and  $30.42 \pm 7.32$  kg/m<sup>2</sup> in the conventional group, with a nonsignificant difference ( $P = 0.504$ ,  $t = 0.671$ ).

Clinical diagnosis of thyroid disorders was of no significant statistical difference. The mean number of patients diagnosed

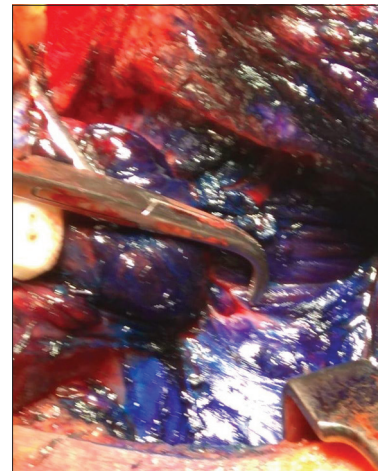


Figure 2: Recurrent laryngeal nerve.

Table 1: Demographic data and characteristics of the studied patients

	Total patients <i>n</i> =90	Methylene blue group <i>n</i> =45	Conventional group <i>n</i> =45	Test value	<i>P</i>	Significance
Age (years)						
Mean±SD	38.36±9.25	37.12±8.25	39.6±10.25	1.264 <sup>a</sup>	0.209	NS
Range	26-58	26-57	28-58			
Sex [ <i>n</i> (%)]						
Males	17 (18.9)	8 (17.8)	9 (20.0)	0.073 <sup>b</sup>	0.787	NS
Females	73 (81.1)	37 (82.2)	36 (80.0)			
BMI (kg/m <sup>2</sup> )						
Mean±SD	30.89±6.53	31.35±5.74	30.42±7.32	0.671 <sup>a</sup>	0.504	NS
Range	22.39-43.21	22.39-42.15	23.31-43.21			
Clinical diagnosis [ <i>n</i> (%)]						
Single nodular goiter	77 (85.6)	35 (77.8)	42 (93.3)	5.636 <sup>b</sup>	0.130	NS
Malignant nodule	5 (5.6)	3 (6.7)	2 (4.4)			
Primary toxic	5 (5.6)	4 (8.9)	1 (2.2)			
Secondary toxic	3 (3.3)	3 (6.7)	0			
Calcium level preoperatively						
Mean±SD	9.09±0.19	9.08±0.18	9.10±0.19	0.513 <sup>a</sup>	0.609	NS
Range	8.46-9.35	8.67-9.25	8.46-9.35			

<sup>a</sup>Independent  $t$  test. <sup>b</sup> $\chi^2$  test.

with single nodular goiter, malignant nodule, primary toxic goiter, and secondary toxic goiter in methylene blue group was 35 (77.8%), three (6.7%), four (8.9%), and three (6.7%), respectively, whereas in conventional group was 42 (93.3%), two (4.4%), one (2.2%), and 0 (0.0%), respectively ( $P = 0.130, t = 5.636$ ).

The mean preoperative calcium level in methylene blue group was  $9.08 \pm 0.18$  mg/dl, whereas it was  $9.10 \pm 0.19$  mg/dl in the conventional group, showing no significant difference in the two groups ( $P = 0.609, t = 0.513$ ).

Operative parameters of the two studied groups are plotted in Table 2. There has been no significant difference in the mean surgical duration time, with  $113.25 \pm 20.32$  min in methylene blue group and  $117.32 \pm 19.45$  min in conventional group ( $P = 0.334, t = 0.971$ ). Furthermore, there has been no significant difference in the mean weight of excised specimen between the two groups, with  $118.75 \pm 45.36$  and  $123.64 \pm 38.35$  g in the methylene group and conventional group, respectively ( $P = 0.582, t = 0.552$ ). However, the mean time of hospital stay was of significant difference, as it was  $2.25 \pm 1.36$  and  $3.17 \pm 1.65$  days in methylene group and conventional group, respectively ( $P = 0.005, t = 2.886$ ).

Table 3 shows the postoperative complications in the two study groups (Fig. 3). There has been no significant difference in the number of patients with postoperative complication in both groups, with five (11.11%) patients in methylene blue group and nine (20.00%) patients in conventional group ( $P = 0.169, t = 1.885$ ).

There has been no significant difference in the number of patients diagnosed with postoperative hypoparathyroidism

in both groups, with three (6.67%) and three (6.67%) patients in methylene group and conventional group, respectively ( $P = 1.000, t = 0.000$ ). In addition, the number of patients with postoperative hypocalcemia was of no significant difference, as it was two (4.44%) in methylene blue group and five (11.11%) in conventional group ( $P = 0.237, t = 1.394$ ).

Moreover, there is no significant difference in the number of patients diagnosed with postoperative RLN in both groups, with 0 (0.00) in methylene blue group and one (2.22%) in conventional group ( $P = 1.011, t = 0.314$ ).

However, one patient of the conventional group had RLN injury, in whom unilateral partial injury in carcinoma of thyroid was recorded.

### DISCUSSION

Although mortality and morbidity occurring from thyroidectomy are very rare, possible hazardous intraoperative and postoperative complications could cause a destructive

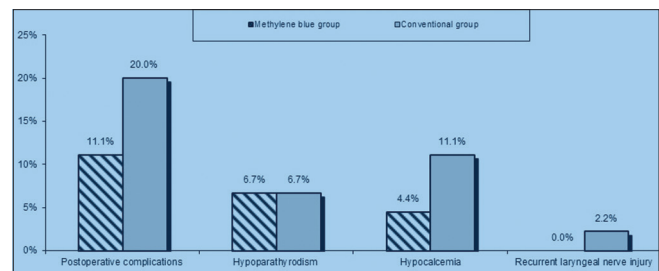


Figure 3: Postoperative complications of the studied groups.

Table 2: Operative parameters of the studied groups

	Total patients n=90	Methylene blue group n=45	Conventional group n=45	Test value <sup>a</sup>	P	Significance
Duration of surgery						
Mean±SD	115.29±19.89	113.25±20.32	117.32±19.45	0.971	0.334	NS
Range	60-132	60-125	60-132			
Weight of excised specimen (g)						
Mean±SD	121.20±41.86	118.75±45.36	123.64±38.35	0.552	0.582	NS
Range	65-163	65-155	68-163			
Hospital stay (days)						
Mean±SD	2.71±1.51	2.25±1.36	3.17±1.65	2.886	0.005	HS
Range	2-6	2-4	2-6			

<sup>a</sup>Independent t test

Table 3: Postoperative complications of the studied groups

	Total n=90 [n (%)]	Methylene blue group n=45 [n (%)]	Conventional group n=45 [n (%)]	Test value <sup>a</sup>	P	Significance
Postoperative complications	14 (15.56)	5 (11.11)	9 (20.00)	1.885	0.169	NS
Hypoparathyroidism	6 (6.67)	3 (6.67)	3 (6.67)	0.000	1.000	NS
Hypocalcemia	7 (7.78)	2 (4.44)	5 (11.11)	1.394	0.237	NS
Recurrent laryngeal nerve injury	1 (1.11)	0	1 (2.22)	1.011	0.314	NS

<sup>a</sup> $\chi^2$  test.

permanent impairment. Currently, hypoparathyroidism and RLN injury are considered the most important and serious complications following thyroidectomy.

The resection degree, the reoperation for complementary surgery, the number of patients operated per surgeon, and the inexperience of the surgeon are considered risk factors for the morbidity of thyroid gland surgery. Specific and meticulous dissection is the keystone in minimizing and lowering the complications incidence [18,19].

A major concern owing to hypoparathyroidism (transient or permanent) leads to long hospital admission with increased cost.

Permanent hypoparathyroidism incidence ranges between 0.4 and 3%, whereas transient hypoparathyroidism ranges between 6.9 and 45%. Overall, 27.9% of transient hypoparathyroidism cases were represented with temporary hypocalcemia, which was rapidly managed by calcium and vitamin D3, as reported by Falk *et al.* [20].

Injury of RLN is the other significant complication in thyroid gland surgery. This leads to major disability to the quality of life [21] and passively affects job performance [22].

RLN palsy incidence rate was 1.8% as reported by Erbil *et al.* [23].

Dralle *et al.* [24] proved that identification of the nerve visually and detection in order to RLN handling is considered as the 'gold standard' of accuracy.

Methylene blue has been used in a wide range in the recent years in sentinel lymph node biopsies [25,26].

Methylene blue spray intraoperatively can be used to perform safe thyroidectomy. Parathyroid gland wash-out time has been after 3 min, whereas for thyroid glands was after 15 min and perithyroid after 25 min. RLN was not stained (white color) [17].

Sari and colleagues concluded no operative mortality and no major complications with using methylene blue spray intraoperatively to do safe thyroidectomy.

Moreover, the mean of age was 44.5 years and sex ratio 47 : 9.

Moreover, transient hypoparathyroidism was seen in 5%, and only three cases had temporary hypocalcemia. Permanent vocal cord paralysis or hypoparathyroidism did not occur. Hospital stay was 1–3 days.

In our study, methylene blue dye which is used to detect the important structure is considered a cheap material. The technique is considered safe and easy application. Methylene blue stain spraying technique in our study is used not only to detect parathyroid glands but also for detecting RLN and perithyroidal area, in comparison with the intravascular approach, which detects only parathyroid glands.

In the current study, parathyroid gland wash-out time was after 3 min, whereas for thyroid glands was after 15 min, and perithyroid after 25 min. RLN was not stained (white color).

The explanation for time difference refers to lymphovascular pattern of different body tissues from the histological point of view parathyroid glands [17].

Traditional RLN is identified during surgery by its anatomical relationship with tracheoesophageal groove, ligament of Berry, and inferior thyroid artery as anatomical landmarks.

Once RLN identification is established, nerve branches can safely be detected via its whole course till it enters the larynx.

After identification of parathyroid glands by our technique, meticulous and fine dissection to its vascular pedicles can be done to save and protect the glands.

Intraoperative stress could be increased by multiple intraoperative stressors, for example, rising intolerance of physician error, medical insurers, and potential legal issues.

Regarding patients' epidemiological characteristics, there has been no significant difference in the mean age of patients (years) in methylene group and conventional group.

Patients' sex had no significant difference in this study. The mean BMI of patients also showed a nonsignificant difference.

Clinical diagnosis of thyroid disorders was of no significant statistical difference.

Regarding the operative parameters of the two studied groups, there has been no significant difference in the mean surgical duration time. Furthermore, there has been no significant difference in the mean weight of excised specimen between the two groups. However, the mean time of hospital stay was of a significant difference.

Regarding the postoperative complications in the two study groups, there was no significant difference in the number of patients with postoperative complication.

There was no significant difference in the number of patients diagnosed with postoperative hypoparathyroidism in both groups. In addition, the number of patients with postoperative hypocalcemia was of no significant difference.

There was no significant difference in the number of patients diagnosed with postoperative RLN injury.

## CONCLUSION

Identification and saving of RLN and parathyroid glands are considered important targets to the surgeons during thyroid surgery. Identification of them lowers level of stress for the surgeon. Using methylene blue spray intraoperatively to do safe thyroidectomy depends on identification of the important nearby thyroid structures such as RLN and parathyroid glands by direct visualization of them for safe and unharmed thyroid surgery.

This technique is still in need of further applications and surgery performances to assess and confirm the effectiveness and reliability of the procedure.

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**Conflicts of interest**

There are no conflicts of interest.

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