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Recurrent laryngeal nerve identification in thyroidectomy by intraoperative staining with methylene blue

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Abstract:
Background: Unrecognized transection of the recurrent laryngeal nerve (RLN) or its motor branch could result in an unexpected permanent palsy. So, for a safe thyroid operation, intraoperative assurance of anatomical and functional RLN integrity is a necessity. Aim of work: To evaluate the recognition and protection of RLN by staining the RLN intraoperatively with methylene blue (MB) in one side and comparing it with the identification alone in the other side visually during total thyroidectomy. Subjects and methods: A case control study (retrospective study) carried out in the department of surgical oncology Zagazig university hospitals and Ismailia teaching oncology hospital during the period from November 2018 to August 2019. The study included 112 patients with bilateral thyroid disease who will do total thyroidectomy. The patients were subdivided into two groups depending on the MB use. Complete history taking was taken from all subjects. General examination of all body systems and local examination of the neck were done. We also did full lab investigations, neck U/S then the operations were performed. Results: We detected transient vocal cord palsy 10 sides (8.6%) of visual identification alone, while in MB sides no case was detected with the same lesion. Conclusion: Recognition of RLN intraoperatively by MB staining is cheap and widely available technique and can decrease the stress during thyroidectomy, especially when Intra Operative Nerve Monitoring (IONM) is absent.
Keywords: Methylene blue, Thyroidectomy, RLN, Surgery.

Introduction:

Visual RLN identification during thyroidectomy seems to be related to lower incidence of RLN palsy. However, it does not ensure success towards a consequence of postoperative vocal cord paralysis. Vocal cord palsy may occur in three to five per cent of all patients after thyroidectomy. IONM has been implemented to minimize this complication, but its use remains contentious. **[1]**

In addition, most injuries of the RLN are not noted intraoperatively. However, the potential reasons of RLN injury may be due to clamping, transection, electro thermal injury, stretching, ligature entrapment or ischemia. **[2]**

Variations in the anatomy of the RLN represent a major cornerstone in the incidence of the injury of the nerve that may be due to visual errors. **[3]**

So, for a safe thyroid operation, intraoperative assurance of anatomical and functional RLN integrity is a necessity. It also played a great role in developing advanced thyroid surgery. Identification of RLN intraoperatively is widely realized during surgical interventions that put this essential neural structure at a threat for iatrogenic injury. **[4]**

In a modification of that, MB can be used intraoperatively to stain nerve fibers which is an old technique used to clear branches of vagus nerve and some other nerves during different surgical interventions. **[5]**

Aim and objectives: To evaluate the recognition and protection of RLN by staining the RLN intra-operatively with methylene blue (MB) in one side and comparing it with the identification alone in the other side visually during total thyroidectomy.

Subjects and methods:

Technical design: A case control study (retrospective study) carried out in the department of surgical oncology Zagazig university hospitals and Ismailia teaching oncology hospital during the period from November 2018 to August 2019. The study included 112 patients with bilateral thyroid disease who will do total thyroidectomy. The patients were subdivided into two groups; Group I (Patient group) in whom we used intraoperative MB staining in one lobe (112 lobes) while Group II (Control group) in whom we did not use intraoperative MB in the other lobe (112 lobes). Inclusion criteria involved patients who approved to share in the study and were diagnosed bilateral benign thyroid disease. On the other hand, exclusion criteria involved patients who refused to share in the study or with repeated thyroid surgeries, malignancy, or preoperative paresis of the vocal folds.

Methods: All patients were subjected to complete history taking. General examination for all body systems and local examination of the neck were done. We also did full lab investigations as CBC, PT, PTT, INR. Liver, kidney, and thyroid function tests were also evaluated. Neck U/S was done then the operations were performed with left or right MB application. (Figure 1, 2)

Figure (1): Total thyroidectomy with LT MB application.

Figure (2): Total thyroidectomy with RT MB application.

Administrative considerations: Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (Institutional Research Board IRB). The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis:

Statistical analysis was performed using SPSS for Windows version 20.0. Data was presented as range, mean and standard deviation (for parametric variables), number and proportion (for categorical variables). Difference between two groups was analyzed using independent sample t-test (for parametric variables) or Mann- Whitney test (for categorical data). Association between variables were estimated using Spearman's rank correlation coefficient. Significance level was set at 0.05. We used Box-and whisker plot to better understand how values are spaced out in different sets of data and display the full range of variation, the likely range of variation (IQ range) and a typical value (the median). In the box plot the central rectangle spanned the first quartile to the third quartile (IQ range). A segment inside the rectangle is the median and whiskers above and below the box showed the location of maximum and minimum values. We used receiver operating characteristic (ROC) curves to determine a cutoff value. The optimal value of the cut-off point is thus obtained when the sum of sensitivity and specificity is at its maximum. We also calculated the sensitivity, specificity, positive predictive value, and negative predictive value.

Results:

Table (1): Demographic data of the studied patients:

Demographic data	Studied patients (N=112)	
	No.	%
Sex		
Male	43	38.4%

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Female	69	61.7 %
Age groups (years)		
20 -	24	21.4 %
30 -	41	36.6%
40 -	31	27.7%
≥ 50	16	14.3%
Age (years)		
Mean ± SD	37.59 ± 16.18	
Median (Range)	35(20-55)	

Qualitative data was represented as number and percentage.

Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR)

Table (1) reveals the demographic data of the studied subjects. This table shows that the mean age of the studied patients is 57.59 ± 16.18 years old, with a range from 20 to 55 years old. The most common age group was 30 to 40 years (41 patients, 36.6%), about 1/3 of the studied patients were male (38.4 %).

Table (2): Characteristics of thyroid lesion:

Bilateral thyroid disease	**Studied patients (N=112)**	
	No.	**%**
Thyroid lesion		
Multinodular goiter	86	76.8 %
Thyroid adenoma	16	14.3%
Graves' disease	10	8.9%

Qualitative data was represented as number and percentage

Table (2) shows the characteristics of thyroid lesion. A bilateral thyroid disease was found in all patients; 86 multinodular goiters (76.8%), 16 thyroid adenoma (14.3%) and 10 Graves' disease (8.9%).

Table (3): Operative duration for each side (lobe):

Operation time (Min)	**MB staining**	**Without MB staining**	**t-test**	**p-value**
Mean ± SD	**27 ± 3.6**	**32 ± 4.5**	**-6.49**	**<0.0001* (HS)**

MB: methylene blue

T-test, P value < 0.5 highly significant (HS)

Table (3) shows the time of the operation for each side (lobe). It was found that the mean time of lobectomy with only RLN visual identification was 32 ± 4.5 min, but it was 27 ± 3.6 min with use of MB, with statistically significant difference (t = - 6.49, P < 0.0001).

Table (4): Postoperative vocal cord palsy for each side (lobe):

vocal cord palsy	**MB staining**	**Without MB staining**	χ^2	**p-value**
Mean ± SD	0 (0.0%)	10 (8.9%)	10.47	0.001* (HS)

$\chi 2$: Chi-square test

Table (4) demonstrates the vocal cord palsy after the operation for each side or lobe. Transient vocal cord palsy was identified in 10 sides (8.6%) of only visual identification, but in MB sides, no case had the same lesion, with statistically significant difference (P = 0.001).

Discussion:

Recognition of peripheral nerves intraoperatively with MB has been used to demonstrate nerve details at many surgical interventions. MB aided to clear even tiny nerve structures to protect postoperative organ functions at many aspects. **[6]**

Several authors discovered that MB dye was oxidized faster by small nerve fibers than connective tissue or muscles so selectively showed blue stain. MB was used during selective vagotomy to identify the vagus nerve and its branches. It has been also used in parotidectomy to identify the facial nerve and its branches. After post-traumatic neuroma removal, MB was used to clear nerve stumps to find healthy fascicular structures during secondary peripheral nerve repair. **[7]**

Our study aimed to evaluate the recognition and protection of RLN by staining the RLN intra-operatively with methylene blue (MB) in one side and comparing it with the identification alone in the other side visually during total thyroidectomy.

In our study, MB was applied in the concentration of 2: 8 (MB: saline solution) (2%), which is known as the optimal concentration. Seif and colleagues used the same concentration as MB concentration was 0.05%. **[8]**

In the study of Nofal and colleagues, transient biochemical hypocalcemia was found in (6.5%) while our study reported 8 cases (7.1). We found no complications from MB in our study and this ensures that MB staining is safe. No interval change is found between Nofal's study and this study in the meantime of operation and also vocal cord palsy. **[9]**

We observed that the dissection was relatively easier and faster with use of MB. Tight control of the nearby vessels resulted in less amount of bleeding and clearer fields, less exposure to retraction, compression, or affection by heat, that represent the principal reasons of transient RLN palsy.

RLN recognition intraoperatively with MB during thyroidectomy is cheap. It is also beneficial to minimize the incidence of RLN palsy. It could improve surgeons' skills. The ideal concentration of MB for nerve staining during thyroidectomy is (2 MB : 8 saline). **[10]**

Conclusion:

Recognition of RLN intraoperatively by MB staining is cheap and widely available technique and can decrease the stress during thyroidectomy, especially when IONM is absent.

Recommendations:

Considering that MB is safe and cheap method for nerve identification, we recommend using it in other operations for nerve identification as superficial parotidectomy, neck dissection and axillary clearance.

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