MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.3.298.303

A Study on Intraoperative Identification of Parathyroid Glands and Recurrent Laryngeal Nerves during Thyroid Surgery Using Methylene Blue Spray: A Randomized Control Trial

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ABSTRACT

Thyroidectomy, a common procedure in iodine-deficient regions, poses risks of recurrent laryngeal nerve (RLN) injury and parathyroid gland damage. Intraoperative techniques, such as methylene blue spraying, are crucial for minimizing complications. To evaluate post-operative vocal cord mobility and assess signs of hypocalcemia. A randomized study at Sri Venkateshwaraa Medical College and Research Centre (October 2017 to May 2018) included 60 patients undergoing conventional thyroidectomy (Group 1) or methylene blue spraying (Group 2). Methylene blue was applied before inferior pole ligation to identify RLN, parathyroid and vascular structures. Postoperative assessments included serum calcium levels and repeat laryngoscopic examination. Predominant preoperative diagnoses were multinodular goitre and papillary carcinoma in both groups. Group B showed significantly higher postoperative calcium levels (9.46±0.13 vs. 8.14±0.18; p<0.0001). Preoperative parathyroid hormone (PTH) levels were comparable (Group A: 20.7±8.08, Group B: 21.12± 8.37). Notably, Group B exhibited a significantly higher mean postoperative PTH level (19.72±1.67; p = 0.001). Complications in Group A had an overall incidence of 16.7%, with 3 out of 5 patients showing recovery in vocal cord mobility at the 6-month follow-up. Methylene blue spraying is a safe and effective method for identifying and protecting RLN and parathyroid glands during thyroidectomy.

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Key Words

Intra operative Identification, parathyroid glands, recurrent laryngeal nerves

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Received: 26 January 2024
Accepted: 16 February 2024
Published: 6 March 2024

Citation: Sathishkumar Lakshmanan, Elakkiya Selvaraj, A. Muzamil Ahmed, Vinothkumar Gunasekaran ,2024. A Study on Intraoperative Identification of Parathyroid Glands and Recurrent Laryngeal Nerves during Thyroid Surgery Using Methylene Blue Spray: A Randomized Control Trial. Res. J. Med. Sci., 18: 298-303, doi: 10.36478/makrjms.2024.3.298.303

INTRODUCTION

Disorders of the thyroid gland constitute the second most common endocrine disease following diabetes mellitus. Thyroid disorders are prevalent in India, with an estimated 42 million people affected by various thyroid diseases. Common thyroid disorders in India include hypothyroidism, hyperthyroidism, goiter and iodine deficiency disorders, Hashimoto's thyroiditis and thyroid cancer and the surgical options include total thyroidectomy, subtotal thyroidectomy and hemi thyroidectomy[1]. Studies have shown a high prevalence of hypothyroidism in adults across different cities in India, with rates ranging from 8.88% to 21.67%[2]. The National Cancer Registry Program in India noted 5614 cases of thyroid cancer between 1984 and 1993, with a higher prevalence among females[3]. Recurrent laryngeal nerve injury and damage to the parathyroid glands are two prevalent complications associated with thyroid surgery. Injuries to the recurrent laryngeal nerve may result in hoarseness, alterations in voice quality, or complete loss of voice, with transient occurrences in 1% to 30% of patients and permanent injuries in 0.5% to 5%[4]. Implementing careful surgical techniques and utilizing intraoperative in-vivo statining, when feasible, can help minimize these complications. Despite the low overall incidence of recurrent laryngeal nerve palsy, when it does occur, it represents a profound and lifelong handicap. Recognizing the anatomy of the recurrent laryngeal nerve has long been acknowledged as the safest approach to reduce nerve injury rates.

In contrast, impairment of the parathyroid glands may result in hypoparathyroidism, characterized by decreased blood calcium levels in 20–30% of individuals following thyroid surgery with studies reporting an incidental parathyroidectomy rate of 15% and an 18% incidence of low postoperative parathyroid hormone (PTH) after total thyroidectomy[4,5]. Current Guidelines for preventing parathyroid gland injuries during thyroid surgery emphasize anatomical landmarks, however challenges in differentiation to separate from the surrounding fat and lymph nodes, contribute to postoperative hypocalcemia. Other techniques to identify the parathyroid gland during thyroidectomy include anatomical guidance[6], partial biopsy(6), Optical Coherence Tomography (OCT)[7], parathyroid-specific luminescence, Fine Needle Aspiration (FNA), blood tests for parathyroid hormone levels and intravenous methylene blue injection[8].

Methylene blue, a medication and dye with over a century of use, is both safe and readily available. In a previous case series, it was observed that methylene blue spray on the surgical field was absorbed by the parathyroid gland faster than in the surrounding perithyroidal area[9].The mechanism of action of methylene blue in identifying parathyroid glands is based on the differential absorption and retention properties of methylene blue by the parathyroid glands compared to adjacent tissues[10]. This safe and effective technique assists surgeons in precisely identifying and avoiding injury to the recurrent laryngeal nerve and parathyroid glands during thyroidectomy. Our study aimed to assess the effectiveness of methylene blue spraying in safely identifying recurrent laryngeal nerves (RLNs) and parathyroid glands during thyroid surgery. Additionally, we sought to determine its overall impact on enhancing the safety of thyroidectomy compared to conventional techniques. Emphasizing the importance of early RLN identification, our findings highlight its role in guiding surgeons to implement precautionary measures and prevent damage during dissection.

Objectives:

- To evaluate the post-operative vocal cord mobility
- To note presence of clinical symptoms or signs of hypocalcaemia

Patients and Methods: This was a prospective, observational study, conducted at the Department of General Surgery, Sri Venkateshwaraa Medical College and Research Centre, Puducherry from November 2017 to September 2019. Institutional Ethical Committee approval and written informed consent was obtained from all cases (SVMCH/IEC/2017/Oct/09).

Study Population: Patients with an indication for thyroidectomy, presenting to the Department of Surgery and ENT, were scheduled for surgery based on their fulfilment of eligibility criteria. All patients who presented with benign and malignant thyroid diseases, willing for surgery under general anaesthesia, belonging to either gender, in the age group of 18-60 years were included in the study. The exclusion criteria were Recurrent thyroid swellings,Preoperative cord dysfunction ,Retrosternal goiter,Patient with history of using antidepressants such as selective serotonin reuptake inhibitors (SSRIs),Hypersensitivity to methylene blue, Patients with renal impairment Pregnancy and breast feeding. A note was made of the patient demographics, type of thyroidectomy done, histopathological diagnosis and complications, if any. In each patient, both before and after surgery, indirect laryngoscopic examination was performed to evaluate vocal cord mobility. The presence of clinical symptoms or signs of hypocalcaemia were noted.

Surgical Procedure: Sixty patients participated with an indication for thyroidectomy. After consenting, the

patients were divided randomly into two groups. Group 1 (control group), Included 30 cases established with the conventional technique. And we will follow up on postoperative complications of hypocalcaemia and symptoms of RLN injuries. Group 2 (interventional group), Included 30 cases established with the methylene blue spraying technique. in this group, we will apply methylene blue spray to identify RLN which will not be stained with dye and to identify the parathyroid gland which will absorb the dye faster than other perithyroidal areas.

After positioning the patient on the operating table, parts were painted with 10% povidone iodine solution and draped. After the standard Kocher incision, total or partial thyroidectomy was performed according to the need. Following the elevation of flaps, lateral thyroid vein ligation and dissection of thyroid lobes were done. The superior pole was ligated and cut. Normally, at this stage, the identification of RLN or the parathyroid is difficult. Before inferior pole ligation, the thyroid lobe was deviated medially and 0.5 mL methylene blue diluted with 5 mL normal saline was sprayed over the thyroid lobe and perilobar area. The major structures in this area include RLN, parathyroid, inferior thyroid artery and veins which were observed post spraying. The surgical specimen was subjected for histopathological examination. Postoperatively, serum calcium levels were estimated between the second to fifth postoperative days. Hypocalcaemia was defined as a serum calcium level less than 8 mg/dL. A repeat indirect laryngoscopic examination was carried out to assess vocal cord mobility postoperatively.

Statistical Analysis: Data were collected, coded, revised and entered using the Statistical Package for the Social Sciences (IBM SPSS) version 23 software. The quantitative data were presented in the form of mean, standard deviation and ranges. Comparison between different groups regarding categorical variables was tested using Pearson Chi-Square (X2) and Fisher's exact test. P value of 0.05 or less was considered significant.

RESULTS AND DISCUSSION

In this study, a total of 60 patients were randomly selected and categorized into two groups: Group A comprising 30 patients, the standard surgery group, and Group B with 30 patients, the methylene blue spray group. The age distribution ranged from 21 to 60 years with a mean age of 41±7 in both groups. Statistical analysis indicated no significant difference between the two groups concerning age and sex (Table 1). Furthermore, there was no substantial distinction in the nature of lesions, with the majority involving benign lesions (83.3% in Group A and 80% in Group B). The proportions of left hemithyroidectomy and right hemithyroidectomy were comparable between the groups (p-value = 0.901). Predominant preoperative diagnoses in both groups included multinodular goitre (46.7% in Group A and 50% in Group B) and papillary carcinoma (16.7% in both groups). Less frequent diagnoses included medullary carcinoma (3.3% in Group A) and follicular carcinoma (3.3% in Group A and 6.7% in Group B) (Table 2). Pre-operative calcium levels exhibited a similar mean in both groups, with the majority falling within the 7.5-9.5 range. Post-operative calcium levels were significantly higher in Group B (9.46±0.13) compared to Group A (8.14±0.18) ($p<0.0001$). Pre-operative parathyroid hormone (PTH) levels showed no significant difference between the groups (20.7±8.08 in Group A and 21.12±8.37 in Group B) (Table 3).

However, post-operatively, Group B exhibited a higher mean PTH level at 19.72±1.67, which was statistically significant ($p = 0.001$), indicating notable differences in post-operative outcomes (Table 4). The table highlights post-operative complications related to the recurrent laryngeal nerve (RLN) and parathyroid glands (PTG) in Group A, with an overall incidence of 16.7%. The assessment of vocal cords was done at the time of extubation using indirect laryngoscopy and was subsequently followed up after 6 months(Table 5).The examination of vocal cords in Group A revealed that out of the 5 patients experiencing RLN complications, 3 exhibited recovery at the 6-month mark, displaying mobile vocal cords. Post-thyroidectomy complications are not uncommon, with risk factors including the extent of resection, reoperation for completion, patient volume per surgeon and the surgeon's experience. Meticulous dissection is crucial in minimizing complications. Postoperative hypoparathyroidism has medical and financial implications, leading to longer hospitalization periods and increased costs[11]. Early complications of thyroidectomy include hypoparathyroidism, hematoma, infection and temporary recurrent laryngeal nerve palsy. Rates of these complications vary between total thyroidectomy and subtotal thyroidectomy procedures[12]. Meticulous dissection is a key factor in minimizing the development of complications[13]. The important factor in thyroid surgery for benign conditions is the extent of resection, as it was believed that total thyroidectomy leads to a higher chance of injury to RLN or the parathyroids as opposed to partial thyroidectomies[9]. The incidence of RLN palsy ranges from 1.5% to 15%[14]. A study reported that RLN palsy occurred in 4.9% of thyroidectomies, with 64.6% being temporary and 35.4% persistent. Intraoperative nerve monitoring (IONM) has been associated with a decreased risk of RLN injury during thyroidectomy[15]. The incidence of

Table 1: The Demographic Characteristics and Nature of lesions of the study participants (n=60).

Parameters	Group A (N = 30) Mean± SD	Group B (N = 30) Mean± SD	p-value
Age (in years)	41.6±7.7	41±7.4	0.323
Gender	N (%)	N (%)	
Male	8 (26.7%)	9 (30%)	0.774
Female	22 (73.3%)	21 (70%)	
Nature of Lesion			
Benign	25 (83.3%)	24 (80%)	0.3637
Malignant	5 (16.7%)	6 (20%)	
Type Of Surgery			
Left Hemithyroidectomy	4 (13.3%)	3 (10%)	0.901
Right Hemithyroidectomy	7 (23.33%)	8 (26.67%)	
Total Thyroidectomy	19 (63.3%)	19 (63.3%)	

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS) *: Chi-square test; •: Independent t-test

Table 2: Comparison of diagnosis between study group (N=60)

Diagnosis	Study Group Group A (N = 30)	Group B (N = 30)
Multinodular goitre	14 (46.7%)	15 (50%)
Papillary carcinoma	5 (16.7%)	5 (16.7%)
Right solitary thyroid nodules	5 (16.7%)	3 (10%)
Left solitary thyroid nodules	4 (13.3%)	5 (16.7%)
Follicular carcinoma	1 (3.3%)	2 (6.7%)
Medullary carcinoma	1 (3.3%)	0 (0%)
Total	30 (100%)	30 (100%)

Table 3: Comparison of Pre-Operative and Post-Operative Calcium Levels Between Study Groups (N=60)

	<7.5	7.5-9.5	>9.5	Mean±SD	
Post-Operative Calcium	N(%)	N(%)	N(%)		p-value
Group A	0	28 (46.7)	2 (3.3)	8.57±0.69	1.000
Group B	0	28(46.7)	2 (3.3)	8.66±0.69	
Post-Operative Calcium					
Group A	7 (23.3%)	22 (73.3%)	1 (3.3%)	8.14±0.18	<0.0001
Group B	0	18 (60%)	12 (40%)	9.46±0.13	

Table 4: Comparison of Pre-Operative and Post-Operative Parathyroid Hormone (PTH) Levels Between Study Groups (N=60)

	<10pg/ml	10-65pg/ml	>65pg/ml		
Pre-operative PTH	N(%)	N(%)	N(%)	Mean	p-value
Group A	0	30 (50%)	0	20.7±8.08	0.827
Group B	0	30 (50%)	0	21.12±8.37	
Post-operative PTH					
Group A	5 (3.3%)	28 (46.7%)	0 (0%)	15.9±0.90	0.001
Group B	1(1.7%)	29 (48.3%)	0 (0%)	19.72±1.67	

Table 5: Postoperative Complications Related to Recurrent Laryngeal Nerve (RLN) and Parathyroid Glands (PTG) in Study Groups (N = 60)

Post op complications	Group A (n = 30)	Group B (n = 30)
Related to RLN	5 (16.7%)	0
Related to PTG	5 (16.7%)	0

permanent hypoparathyroidism varies depending on factors such as surgical technique, extent of surgery, and patient characteristics. The incidence of permanent hypoparathyroidism requiring calcitriol therapy after total thyroidectomy for Graves' disease was studied in adults over 65, showing an incidence of 7.3. The technique of using dyes in identification of parathyroid glands and prevention of hypoparathyroidism, was first described by Klopper PJ and Moe RE[16]. Initial studies were conducted using dyes like toluidine blue and tryptan blue, however, these were replaced by methylene blue as their teratogenic effects were discovered[17].

Several studies have explored the use of parathyroid staining techniques involving the injection of dyes via intravenous or intra-arterial routes to aid in the identification and preservation of parathyroid glands during thyroid surgery. A clinical study in 1968 described the selective, in vivo staining of parathyroid glands using toluidine blue administered intravenously and intra-arterially in human subjects undergoing surgery for thyroid neoplasm or toxic goiter[18]. Sari *et al*. in 2012 conducted a study where methylene blue was sprayed over the thyroid lobe and perilober area during total thyroidectomy. They observed that the recurrent laryngeal nerve did not stain and remained white, while all other tissues were stained blue. The parathyroid glands washed out the blue stain within a 3 minutes and regained their original yellow color. This technique allowed for the safe identification of both parathyroid glands and recurrent laryngeal nerves, proving to be effective, safe and technically feasible[13]. We obtained similar results in our study also. In all 30 patients, the RLN was visible as an unstained white structure in the blue stained background and could be easily identified. In comparison to our study, Monib et al. achieved intraoperative identification of parathyroid glands in 82% of cases (N=41/50) using methylene blue

spray[11]. Similarly, Farghaly *et al*. reported that the methylene blue spraying technique was effective in RLN identification without recorded injury in 50/50 (100%) versus one case (1/50) suffered from bilateral vocal cord affection in anatomical identification technique[19].

In our study, complications related to the recurrent laryngeal nerve (RLN) and parathyroid glands (PTG) were observed in 16.7% (n=5/30) of Group A cases. Notably, the assessment of vocal cords at extubation and the 6-month follow-up in Group A revealed recovery in 3 out of 5 patients who initially experienced RLN complications. These results support the potential utility of methylene blue spray in mitigating RLN-related complications during thyroid surgery, reinforcing its role in improving patient outcomes.

Limitation: The study is limited by its sample size of 60 patients and a single-center design, potentially limiting the generalizability of the findings. Addressing these limitations in future research can enhance the robustness and applicability of the study's outcomes.

CONCLUSION

Safe thyroid surgery is based on visualization of the parathyroid glands, RLN and thyroid arteries. Methylene blue dye spraying is technically feasible, safe and effective method for identifying and protecting the RLN and parathyroid glands during thyroidectomy. Moreover, it does not require intravenous or intra arterial administration of methylene blue and thus the potential complications of intra vascular dye infusion can be avoided.

Conflict of Interest: The authors declare no conflict of interest.

Sources of Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contribution: Authors contributed equally in the study.

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