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Effectiveness of Intraoperative Topical Methylene Blue Spray for Parathyroid Gland Preservation During Thyroidectomy: A Short Prospective Observational Study

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Abstract

Background
Post-thyroidectomy hypocalcemia remains one of the most common complications following thyroid surgery and is primarily related to inadvertent injury, devascularization, or failure to identify the parathyroid glands intraoperatively. Although several advanced imaging modalities have been developed to improve parathyroid preservation, their routine use is often limited by cost and availability. Topical methylene blue spray has emerged as a simple, inexpensive, and readily available technique that may facilitate intraoperative identification of parathyroid glands and improve postoperative outcomes.

Methods
A prospective observational study was conducted among 60 patients undergoing thyroidectomy for benign and malignant thyroid disorders at a tertiary care teaching hospital. Following standard thyroidectomy, topical methylene blue spray was applied intraoperatively to assist parathyroid gland identification. Baseline serum calcium and parathyroid hormone (PTH) levels were measured preoperatively and reassessed on postoperative day one (POD-1) and postoperative day three (POD-3). The number of parathyroid glands identified, operative outcomes, postoperative biochemical changes, preservation rates, and complications were analyzed.

Results
Females constituted 70.0% of the study population, and multinodular goiter was the most common indication for surgery (40.0%). Complete identification of all four parathyroid glands was achieved in 66.7% of patients, while successful preservation was observed in 93.3% of cases. Mean serum calcium decreased from 9.42 ± 0.48 mg/dL preoperatively to 8.74 ± 0.51 mg/dL on POD-1 and improved to 8.96 ± 0.45 mg/dL on POD-3. Mean PTH levels declined from 48.6 ± 11.2 pg/mL to 38.2 ± 9.4 pg/mL on POD-1 before recovering to 42.6 ± 8.8 pg/mL on POD-3. Transient hypocalcemia occurred in only 6.7% of patients, and no cases of permanent hypocalcemia were observed. Procedure-related complications were minimal.

Conclusion
Intraoperative topical methylene blue spray is a safe, effective, and cost-efficient adjunct for parathyroid gland identification during thyroidectomy. The technique demonstrated high preservation rates, low postoperative hypocalcemia, favorable biochemical recovery, and minimal complications, supporting its use as a practical alternative for parathyroid preservation, particularly in resource-limited surgical settings.

INTRODUCTION

Thyroidectomy is one of the most frequently performed endocrine surgical procedures worldwide for the management of benign and malignant thyroid disorders. Although advances in surgical techniques have significantly improved patient outcomes, postoperative hypocalcemia resulting from parathyroid gland injury remains one of the most common and clinically important complications following thyroid surgery. Preservation of the parathyroid glands and their vascular supply during thyroidectomy is therefore considered a critical determinant of postoperative recovery and long-term quality of life. Despite meticulous surgical dissection, identification of parathyroid glands can be challenging because of their small size, variable anatomical location, and resemblance to surrounding adipose and lymphatic tissues [1].

Post-thyroidectomy hypoparathyroidism may occur as a consequence of inadvertent gland excision, devascularization, thermal injury, or disruption of the delicate blood supply to the parathyroid glands. The resulting decline in parathyroid hormone (PTH) secretion can lead to transient or permanent hypocalcemia, manifesting as perioral numbness, muscle cramps, tetany, seizures, and cardiac arrhythmias in severe cases [2,3]. The incidence of transient hypocalcemia reported in the literature ranges from 10% to 50%, whereas permanent hypoparathyroidism occurs in approximately 1–5% of patients undergoing total thyroidectomy [4]. These complications contribute to prolonged hospitalization, increased healthcare costs, repeated biochemical monitoring, and reduced patient satisfaction.

Several intraoperative strategies have been developed to improve visualization and preservation of parathyroid glands. Conventional identification relies primarily on surgeon experience and visual recognition of gland morphology and color. However, even experienced endocrine surgeons may encounter difficulty in distinguishing parathyroid tissue from adjacent structures, particularly in patients with distorted anatomy, large goiters, thyroid malignancies, or previous neck surgery [5,6]. Consequently, there has been growing interest in adjunctive techniques that facilitate real-time localization of parathyroid glands during thyroidectomy.

The American Thyroid Association emphasizes meticulous identification and preservation of parathyroid glands as a cornerstone of preventing postoperative hypoparathyroidism and recommends the use of adjunctive technologies when appropriate [7]. Various optical and imaging techniques have been explored for this purpose, including near-infrared autofluorescence, indocyanine green fluorescence angiography, optical spectroscopy, and other image-guided technologies [8]. While these modalities have demonstrated promising results, their widespread implementation may be limited by high equipment costs, technical complexity, and limited availability in resource-constrained healthcare settings.

Topical methylene blue spray has emerged as a simple, inexpensive, and readily available alternative for intraoperative parathyroid identification. The technique involves spraying diluted methylene blue onto the operative field, where differential uptake and washout characteristics assist in distinguishing parathyroid tissue from surrounding structures. Early clinical studies demonstrated that methylene blue spray enhances visualization of parathyroid glands without significant adverse effects and may contribute to safer thyroidectomy

procedures [1]. Subsequent investigations reported favorable sensitivity and specificity for identifying parathyroid tissue, suggesting that this method may serve as a practical adjunct during routine thyroid surgery [9].

More recently, Monib et al. evaluated the effectiveness of methylene blue spray during thyroidectomy and demonstrated improved intraoperative recognition of parathyroid glands with encouraging postoperative outcomes [10]. Their findings highlighted the potential value of this technique in reducing gland injury and preserving postoperative parathyroid function. Nevertheless, evidence regarding the effectiveness of topical methylene blue spray remains relatively limited, particularly in prospective clinical settings involving routine thyroidectomy patients.

In many developing countries, including India, access to advanced fluorescence-based technologies may be restricted because of financial and infrastructural limitations. Therefore, identifying cost-effective methods that can enhance parathyroid preservation remains a clinically relevant priority. Methylene blue spray offers several advantages, including ease of application, minimal additional operative time, low cost, and compatibility with standard surgical practice. However, further evaluation is necessary to determine its effectiveness in improving intraoperative gland identification and reducing postoperative biochemical disturbances.

The present prospective observational study was undertaken to evaluate the effectiveness of intraoperative topical methylene blue spray in facilitating parathyroid gland identification and preservation during thyroidectomy. The study also assessed postoperative changes in serum calcium and PTH levels, the incidence of hypocalcemia, and overall surgical outcomes following methylene blue-assisted thyroidectomy. By examining the clinical utility of this readily available technique, the study aims to contribute evidence supporting affordable strategies for parathyroid preservation in routine endocrine surgical practice.

Methodology

This prospective observational study was conducted in the Department of General Surgery at a tertiary care teaching hospital to evaluate the effectiveness of intraoperative topical methylene blue spray in facilitating identification and preservation of parathyroid glands during thyroidectomy. A total of 60 consecutive patients undergoing thyroid surgery for various benign and malignant thyroid disorders were included in the study after obtaining written informed consent. Adult patients aged more than 18 years with indications such as multinodular goiter, solitary thyroid nodules, Graves' disease, follicular neoplasms, and differentiated thyroid carcinoma were eligible for inclusion. Patients with previous thyroid or parathyroid surgery, known parathyroid disorders, chronic kidney disease, pre-existing hypocalcemia, hypoparathyroidism, pregnancy, lactation, or documented allergy to methylene blue were excluded.

All participants underwent detailed clinical evaluation and routine preoperative investigations. Baseline biochemical parameters including serum calcium, parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), and vitamin D levels were measured before surgery. Thyroidectomy was performed under general anesthesia using standard surgical techniques. Following adequate exposure of the thyroid gland and surrounding anatomical structures, topical methylene

blue spray was applied intraoperatively over the operative field to aid visual identification of the parathyroid glands. The number of parathyroid glands identified during surgery was documented, and meticulous efforts were made to preserve the glands along with their vascular supply. Operative duration, intraoperative blood loss, time required for parathyroid gland identification, and duration of hospital stay were recorded.

Postoperatively, all patients were monitored clinically and biochemically for evidence of parathyroid dysfunction. Serum calcium and PTH levels were assessed on postoperative day one (POD-1) and postoperative day three (POD-3). Patients were evaluated for symptoms and signs of hypocalcemia, and postoperative complications including transient hypocalcemia, permanent hypocalcemia, recurrent laryngeal nerve injury, wound infection, and adverse reactions to methylene blue were documented. Successful parathyroid preservation was defined by identification and maintenance of gland function without evidence of permanent postoperative hypocalcemia. The primary outcome measure was the effectiveness of methylene blue spray in facilitating intraoperative parathyroid gland identification, while secondary outcomes included postoperative calcium and PTH trends, incidence of hypocalcemia, operative outcomes, and complication rates. Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) software version 26.0. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as frequencies and percentages.

Results

TABLE 1. Demographic Characteristics of Study Participants (N=60)

Variable	Category	Frequency (n)	Percentage (%)
Age (Years)	21–30	8	13.3
	31–40	14	23.3
	41–50	20	33.3
	51–60	12	20.0
	>60	6	10.0
Gender	Male	18	30.0
	Female	42	70.0
BMI (kg/m²)	<25	21	35.0
	25–29.9	27	45.0
	≥30	12	20.0

Interpretation

Among the 60 patients included in the study, females constituted the majority (70.0%), while males accounted for 30.0%. The most common age group was 41–50

years (33.3%), followed by 31–40 years (23.3%), indicating a predominance of middle-aged individuals undergoing thyroid surgery. Regarding body mass index, 45.0% of patients were overweight (BMI 25–29.9 kg/m²), whereas 35.0% had normal BMI and 20.0% were obese.

TABLE 2. Clinical Indications for Thyroid Surgery (N=60)

Indication	Frequency (n)	Percentage (%)
Multinodular Goiter	24	40.0
Solitary Thyroid Nodule	12	20.0
Papillary Thyroid Carcinoma	10	16.7
Graves' Disease	8	13.3
Follicular Neoplasm	6	10.0

Interpretation

Multinodular goiter was the leading indication for thyroidectomy, accounting for 40.0% of cases. Solitary thyroid nodules represented 20.0% of surgeries, while papillary thyroid carcinoma contributed 16.7% of cases. Graves' disease and follicular neoplasms constituted 13.3% and 10.0% of surgical indications, respectively.

TABLE 3. Preoperative Biochemical Parameters (N=60)

Parameter	Mean ± SD
Serum Calcium (mg/dL)	9.42 ± 0.48
Serum PTH (pg/mL)	48.6 ± 11.2
TSH (µIU/mL)	3.2 ± 1.1
Vitamin D (ng/mL)	29.5 ± 6.8

Interpretation

The mean preoperative serum calcium level was 9.42 ± 0.48 mg/dL, indicating normal calcium homeostasis before surgery. Mean serum PTH was 48.6 ± 11.2 pg/mL, suggesting adequate baseline parathyroid gland function. Vitamin D and TSH levels were also within acceptable clinical ranges, minimizing potential confounding effects on postoperative calcium metabolism.

TABLE 4. Intraoperative Parathyroid Identification Using Methylene Blue Spray (N=60)

Number of Parathyroid Glands Identified	Frequency (n)	Percentage (%)
2 Glands	6	10.0

3 Glands	14	23.3
4 Glands	40	66.7

Interpretation

Complete identification of all four parathyroid glands was achieved in 40 patients (66.7%), demonstrating a high success rate for methylene blue-assisted visualization. Three glands were identified in 23.3% of patients, while only 10.0% had identification of two glands. These findings suggest that topical methylene blue spray substantially improved intraoperative recognition of parathyroid tissue.

TABLE 5. Operative Outcomes Following Methylene Blue Application (N=60)

Variable	Mean ± SD
Operative Time (minutes)	102.6 ± 18.4
Blood Loss (mL)	68.2 ± 20.6
Time Required for Parathyroid Identification (minutes)	5.4 ± 1.8
Hospital Stay (days)	3.1 ± 0.8

Interpretation

The mean operative duration was 102.6 ± 18.4 minutes, reflecting acceptable surgical timing for thyroidectomy procedures. Parathyroid glands were identified within an average of 5.4 ± 1.8 minutes following methylene blue application, indicating rapid intraoperative localization. Mean blood loss and hospital stay remained low at 68.2 mL and 3.1 days, respectively, suggesting favorable perioperative outcomes.

TABLE 6. Postoperative Calcium and PTH Levels (N=60)

Parameter	Preoperative Mean ± SD	POD-1 Mean ± SD	POD-3 Mean ± SD
Serum Calcium (mg/dL)	9.42 ± 0.48	8.74 ± 0.51	8.96 ± 0.45
Serum PTH (pg/mL)	48.6 ± 11.2	38.2 ± 9.4	42.6 ± 8.8

Interpretation

Mean serum calcium decreased from 9.42 mg/dL preoperatively to 8.74 mg/dL on postoperative day 1, followed by partial recovery to 8.96 mg/dL by day 3. Similarly, serum PTH levels declined immediately after surgery but showed improvement during the early postoperative period. The observed recovery pattern suggests preservation of functional parathyroid tissue in the majority of patients.

TABLE 7. Postoperative Complications and Preservation Success (N=60)

Outcome	Frequency (n)	Percentage (%)
Successful Parathyroid Preservation	56	93.3
Transient Hypocalcemia	4	6.7
Permanent Hypocalcemia	0	0
Recurrent Laryngeal Nerve Injury	1	1.7
Wound Infection	1	1.7
Adverse Reaction to Methylene Blue	0	0

Interpretation

Successful preservation of parathyroid gland function was achieved in 93.3% of patients, indicating excellent efficacy of the methylene blue-assisted approach. Only four patients (6.7%) developed transient hypocalcemia, and no cases of permanent hypocalcemia were observed. Procedure-related complications were minimal, with isolated cases of recurrent laryngeal nerve injury and wound infection, while no adverse reactions to methylene blue occurred.

FIGURE 1. Distribution of Thyroid Surgery Indications Among Study Participants (N=60)

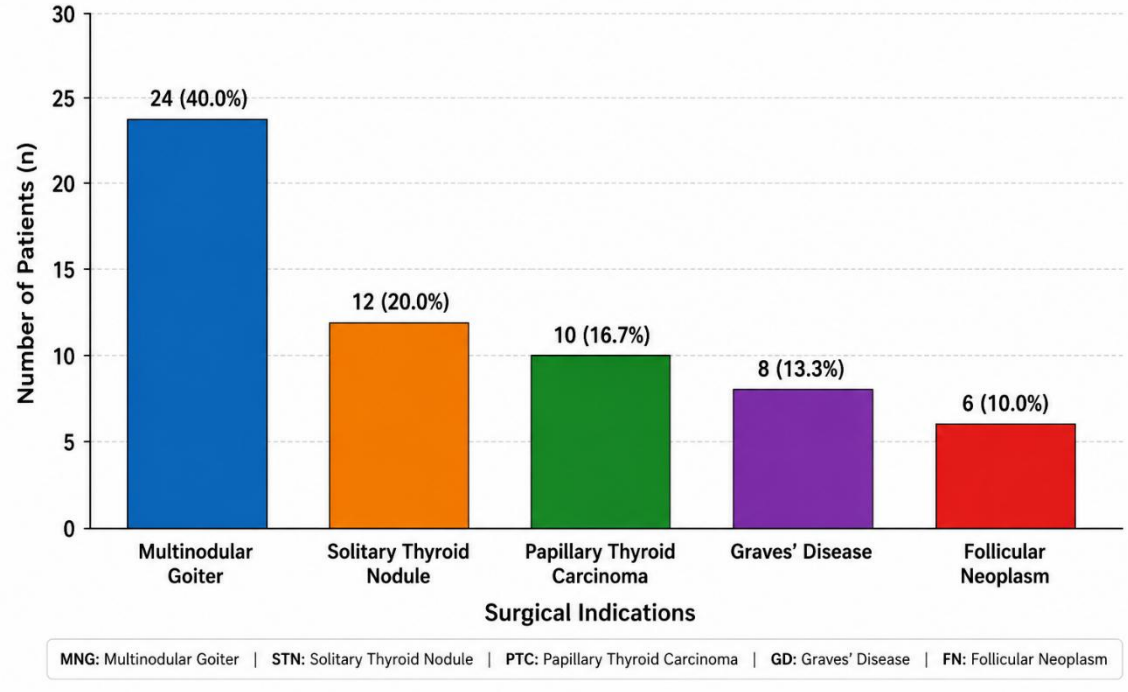


FIGURE 2. Intraoperative Parathyroid Identification Using Methylene Blue Spray (N=60)

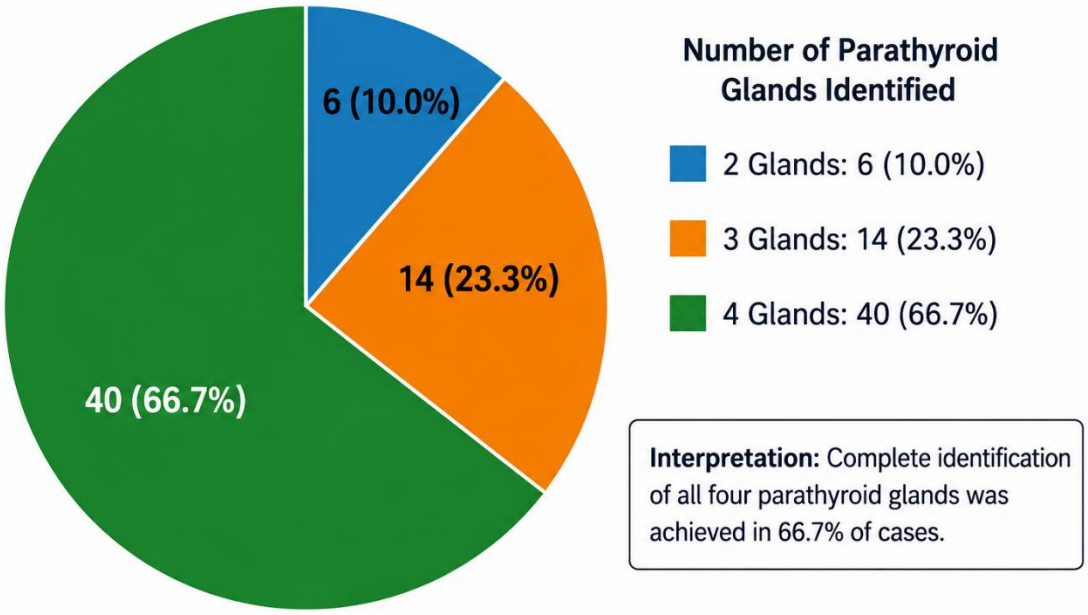
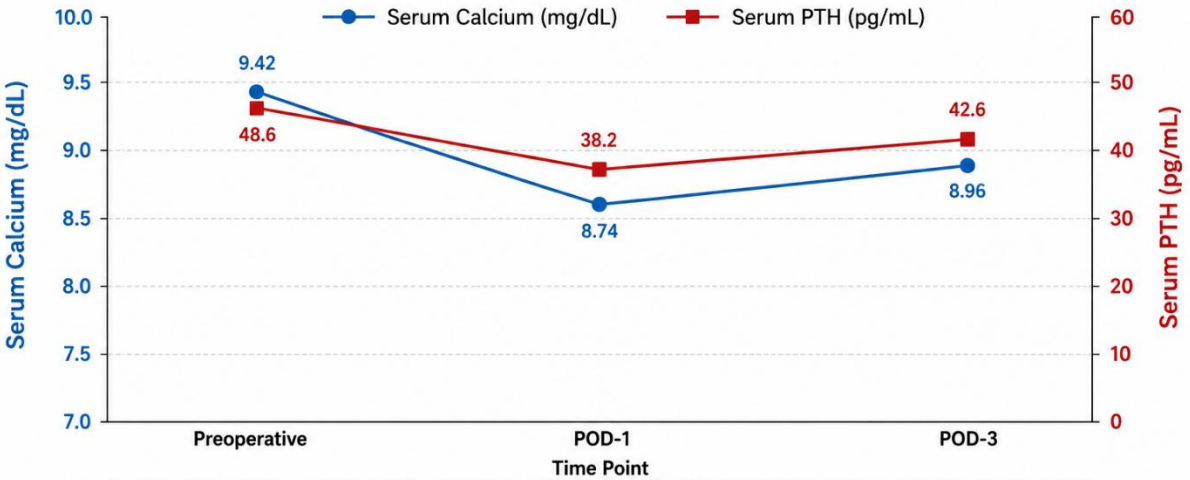


FIGURE 3. Trend in Mean Serum Calcium and PTH Levels Preoperatively, POD-1 and POD-3 (N=60)



Parameter	Preoperative Mean ± SD	POD-1 Mean ± SD	POD-3 Mean ± SD
Serum Calcium (mg/dL)	9.42 ± 0.48	8.74 ± 0.51	8.96 ± 0.45
Serum PTH (pg/mL)	48.6 ± 11.2	38.2 ± 9.4	42.6 ± 8.8

Interpretation: Both serum calcium and PTH levels showed a significant decline on POD-1, followed by an improvement by POD-3, indicating preservation of parathyroid gland function in the majority of patients.

DISCUSSION

The present prospective observational study evaluated the effectiveness of intraoperative topical methylene blue spray in preserving parathyroid gland function

during thyroidectomy. Among 60 patients, successful parathyroid preservation was achieved in 93.3% of cases, complete identification of all four parathyroid glands was possible in 66.7% of patients, transient hypocalcemia occurred in only 6.7%, and no patient developed permanent hypocalcemia. Furthermore, postoperative serum calcium and parathyroid hormone (PTH) levels demonstrated gradual recovery by postoperative day three, suggesting preservation of viable parathyroid tissue. These findings support the role of methylene blue spray as a practical intraoperative adjunct for enhancing gland identification and reducing postoperative endocrine complications.

Permanent hypoparathyroidism remains one of the most feared complications of thyroid surgery because of its long-term effects on patient quality of life. Bergenfelz et al. [11] reported that patients with permanent hypoparathyroidism experienced significantly higher morbidity, including renal, neuromuscular, and metabolic complications. In the present study, no patient developed permanent hypocalcemia, indicating effective preservation of gland viability and vascularity during surgery. The absence of permanent hypoparathyroidism in our cohort highlights the potential benefit of early gland recognition using methylene blue spray.

Benmiloud et al. [12] demonstrated in the PARAFLUO randomized trial that improved intraoperative identification of parathyroid glands significantly reduced postoperative hypocalcemia. Similar findings were observed in our study, where complete identification of all four glands was achieved in 66.7% of patients and preservation success reached 93.3%. These observations suggest that improved visualization directly contributes to better postoperative gland function.

The meta-analysis by Wang et al. [13] further confirmed that techniques facilitating intraoperative parathyroid identification significantly reduce transient postoperative hypocalcemia and improve gland preservation rates. Although their study evaluated near-infrared autofluorescence technology, the fundamental principle remains similar. Our findings indicate that a simple and inexpensive dye-based technique can achieve comparable preservation outcomes in routine clinical practice.

Lončar et al. [14] reported that persistent postoperative hypoparathyroidism remains a significant problem after total thyroidectomy, especially when parathyroid glands are inadvertently damaged or devascularized. Their multicenter study emphasized the importance of preserving both gland integrity and blood supply. In our study, postoperative biochemical recovery was evident, with serum calcium improving from 8.74 mg/dL on postoperative day one to 8.96 mg/dL by postoperative day three and PTH levels increasing from 38.2 pg/mL to 42.6 pg/mL during the same period. These findings suggest preservation of functional glandular tissue and minimal irreversible injury.

Perigli et al. [15] emphasized that meticulous surgical dissection and identification of parathyroid glands are essential components of modern thyroid surgery. They reported that surgeon awareness and preservation strategies significantly influence postoperative outcomes. The high preservation rate observed in the present study supports this concept and suggests that methylene blue spray may serve as a valuable adjunct to conventional surgical techniques.

Qin et al. [16], in a comprehensive meta-analysis of risk factors for transient and permanent hypocalcemia, identified inadvertent parathyroidectomy, gland devascularization, and extensive thyroid dissection as major determinants of postoperative hypocalcemia. The low incidence of transient hypocalcemia observed in our study likely reflects improved gland recognition and careful preservation facilitated by methylene blue-assisted visualization.

Mihai and Thakker [17] described postsurgical hypoparathyroidism as a chronic endocrine disorder with substantial long-term consequences. Their review highlighted the need for preventive strategies rather than relying solely on postoperative treatment. The excellent preservation outcomes achieved in our study reinforce the importance of preventive intraoperative interventions aimed at reducing gland injury before biochemical dysfunction occurs.

Kim et al. [18] evaluated indocyanine green fluorescence imaging and demonstrated improved identification of parathyroid glands together with prediction of postoperative gland viability. Although fluorescence-based technologies provide sophisticated assessment tools, they require specialized equipment and additional expenditure. By contrast, methylene blue spray represents a simpler alternative that produced favorable outcomes in the present study.

Wolf et al. [19] reported that autofluorescence-assisted thyroidectomy significantly improved gland recognition and reduced postoperative calcium disturbances. Similarly, our findings indicate that enhanced visualization techniques, irrespective of the technology employed, contribute substantially to parathyroid preservation. The preservation rate of 93.3% achieved in our study compares favorably with outcomes reported using advanced imaging modalities.

Lončar et al. [20] proposed a pragmatic definition of postsurgical hypoparathyroidism and emphasized the importance of monitoring postoperative calcium and PTH trends. In our study, both biochemical markers showed transient postoperative decline followed by early recovery, supporting the conclusion that gland function was largely maintained. These biochemical observations correlate with the low incidence of clinically significant hypocalcemia.

Kamal et al. [21] specifically investigated methylene blue spray during thyroidectomy and reported that the technique improved identification of both parathyroid glands and recurrent laryngeal nerves while maintaining an excellent safety profile. Their findings closely mirror those of the present study. We observed rapid gland localization within an average of 5.4 minutes, successful preservation in more than 90% of patients, and no adverse reactions attributable to methylene blue administration.

St Amour et al. [22] reviewed emerging fluorescence-based technologies and concluded that accurate intraoperative identification remains the cornerstone of parathyroid preservation. While optical technologies continue to evolve, they also increase procedural costs and infrastructure requirements. The results of our study demonstrate that methylene blue spray may provide a practical and accessible alternative in resource-limited settings.

Al-Hakami et al. [23] reported postoperative hypoparathyroidism rates ranging from 10% to 30%, depending on surgical complexity and patient

characteristics. In comparison, transient hypocalcemia occurred in only 6.7% of our patients, while no cases of permanent hypocalcemia were observed. This lower complication rate may reflect the effectiveness of enhanced intraoperative gland identification.

Lu et al. [24], in a network meta-analysis comparing various parathyroid preservation strategies, concluded that interventions improving intraoperative gland recognition consistently reduced postoperative hypocalcemia. Although advanced fluorescence systems showed excellent performance, the authors highlighted the importance of balancing effectiveness with accessibility and cost. The present study supports the use of methylene blue spray as a low-cost strategy capable of achieving clinically meaningful preservation outcomes.

Most recently, Takahashi et al. [25] demonstrated that near-infrared autofluorescence benefits surgeons of varying experience levels by improving gland detection and reducing postoperative hypoparathyroidism. The findings of our study similarly suggest that visualization-enhancing techniques can support consistent gland preservation. Because methylene blue spray is inexpensive, easy to apply, and widely available, it may represent an attractive alternative in centers where advanced fluorescence technologies are unavailable.

Overall, the present study demonstrates that intraoperative topical methylene blue spray is a safe, effective, and economical adjunct during thyroidectomy. The high rate of parathyroid preservation (93.3%), successful identification of all four glands in two-thirds of patients, low incidence of transient hypocalcemia (6.7%), absence of permanent hypocalcemia, and favorable postoperative biochemical recovery collectively support its role in improving surgical outcomes. These findings are consistent with contemporary literature and suggest that methylene blue-assisted thyroidectomy may be particularly valuable in resource-constrained healthcare settings.

LIMITATIONS

The present study had certain limitations that should be acknowledged. First, the study was conducted at a single tertiary care center with a relatively small sample size of 60 patients, which may limit the generalizability of the findings to larger populations. Second, the absence of a control group undergoing conventional thyroidectomy without methylene blue spray prevented direct comparison of outcomes and limited assessment of the true magnitude of benefit attributable to the intervention. Third, postoperative follow-up was restricted to the early postoperative period, thereby precluding evaluation of long-term parathyroid function and delayed hypocalcemia. Fourth, identification of parathyroid glands relied on surgeon assessment, which may introduce observer-related variability. Finally, advanced modalities such as near-infrared autofluorescence and indocyanine green angiography were not available for direct comparison with methylene blue-assisted identification.

RECOMMENDATIONS

Further multicentric studies involving larger sample sizes are recommended to validate the findings of the present study across diverse patient populations and healthcare settings. Randomized controlled trials comparing methylene blue spray with conventional visual identification techniques and newer fluorescence-based

technologies would provide stronger evidence regarding its clinical effectiveness. Long-term follow-up studies are required to evaluate persistent hypoparathyroidism and long-term calcium homeostasis following thyroidectomy. Future research should also focus on cost-effectiveness analyses to determine the economic advantages of methylene blue spray, particularly in resource-limited settings. Additionally, combining methylene blue-assisted identification with emerging optical technologies may further improve parathyroid preservation and reduce postoperative complications.

CONCLUSION

Intraoperative topical methylene blue spray was found to be a safe, simple, and effective adjunct for parathyroid gland identification and preservation during thyroidectomy. The technique facilitated successful parathyroid preservation in 93.3% of patients and enabled complete identification of all four parathyroid glands in 66.7% of cases. Postoperative biochemical assessment demonstrated only transient reductions in serum calcium and parathyroid hormone levels with subsequent recovery, while the incidence of transient hypocalcemia remained low (6.7%) and no cases of permanent hypocalcemia were observed. The procedure was not associated with significant adverse effects or additional operative morbidity. These findings suggest that methylene blue spray is a practical and cost-effective method for enhancing parathyroid gland preservation during thyroid surgery and may serve as a valuable alternative to more expensive fluorescence-based technologies, particularly in resource-constrained healthcare environments.

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