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Accuracy of Axillary Sentinel Lymph Node Biopsy Using Methylene Blue Injection Technique in Early Breast Cancer: A Cross-Sectional Study

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A B S T R A C T

Background: Sentinel lymph node biopsy (SLNB) is the standard staging procedure for early-stage, clinically node-negative breast cancer, often replacing axillary lymph node dissection (ALND). Methylene blue dye (MBD) offers a cost-effective alternative to radioisotopes, particularly in resource-limited settings.
Objective: This study evaluated the efficacy of SLNB using the MBD injection technique in early breast cancer patients.
Methods: A cross-sectional study was conducted at SIMS&RC from June 2023 to September 2024, involving 40 patients with T1/T2 breast tumors and no clinical or radiological axillary lymph node involvement. SLNB was performed using MBD, followed by histopathological evaluation. Identification rate, accuracy, sensitivity, specificity, predictive values, and false-negative rate were calculated.
Results: The identification rate was 100%, with an accuracy of 94.73%. Sensitivity was 93.75%, specificity was 100%, positive predictive value (PPV) was 100%, negative predictive value (NPV) was 75%, and the false-negative rate was 6.25%. Of the 40 patients, 85% underwent mastectomy, and 15% had breast-conservative surgery. SLN positivity was confirmed in 37.5% of cases on histopathology.
Conclusion: The MBD technique demonstrated high accuracy and reliability for SLNB in early breast cancer, supporting its use in settings lacking nuclear medicine facilities. Its low false-negative rate and cost-effectiveness make it a viable alternative.

Keywords: Sentinel lymph node biopsy, methylene blue dye, early breast cancer, axillary staging, accuracy.

INTRODUCTION

Breast cancer remains a leading cause of morbidity and mortality globally, with an estimated 2.3 million new cases reported in 2020 [1]. In India, it accounts for 13.5% of all cancer cases and 10.6% of cancer-related deaths, with a cumulative risk of 2.81% [2]. Early detection and accurate staging are critical for optimizing treatment and improving survival outcomes. Axillary lymph node status is a key prognostic factor, influencing decisions on adjuvant therapies and predicting overall survival [3]. Historically, axillary lymph node dissection (ALND) was the standard approach for staging, but it is associated with significant morbidity, including lymphedema (10–52%), nerve injury (15–30%), and chronic pain [4].

Sentinel lymph node biopsy (SLNB) has emerged as a less invasive alternative, identifying the first lymph node(s) draining a tumor—termed the sentinel lymph node (SLN)—to assess for metastasis [5]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial demonstrated SLNB's efficacy, reporting an accuracy of 97.1% and a false-negative rate (FNR) of 9.8% when using dual techniques (radioisotopes and blue dyes) [6]. However, the

availability of radioisotopes and nuclear medicine facilities is limited in non-metropolitan and resource-constrained regions, prompting exploration of simpler, cost-effective methods such as blue dye alone [7].

Methylene blue dye (MBD) has gained attention for its accessibility, low cost, and minimal side effects compared to radioisotopes or other dyes like isosulfan blue [8]. Studies have shown that MBD alone can achieve identification rates exceeding 90%, making it a practical option in settings where advanced infrastructure is unavailable [9]. For instance, Gupta et al. reported comparable oncological outcomes using MBD alone versus combined techniques, with reduced morbidity compared to ALND [10]. Similarly, Hermansyah et al. found MBD to have a favorable identification rate and predictive value in early breast cancer [11].

The rationale for SLNB lies in its ability to spare patients unnecessary ALND when the SLN is negative, as axillary metastasis is absent in 93–95% of T1 and 50–75% of T2 tumors [12]. This is particularly relevant in India, where breast cancer incidence is rising, and healthcare resources are unevenly distributed [13]. Despite its advantages, the efficacy of MBD as a standalone technique requires further validation, especially in diverse populations and smaller cohorts. Variability in FNRs across studies (ranging from 5–10%) underscores the need for institution-specific data to establish reliability [14].

This study builds on prior research by evaluating the MBD injection technique in a cohort of Indian patients with early breast cancer. Conducted at a single center, it aims to provide evidence on its accuracy, sensitivity, and feasibility in a resource-limited context. By comparing our findings with existing literature, we seek to contribute to the growing body of evidence supporting MBD's role in SLNB, potentially reducing the reliance on radioisotopes and improving patient outcomes [15]. The following sections detail the study's objectives, methodology, results, and implications within the broader scientific framework.

AIMS

The primary objective of this study was to determine the efficacy of axillary sentinel lymph node biopsy using the methylene blue injection technique in patients with early-stage (T1 and T2) breast cancer. Specific goals included assessing the identification rate, accuracy, sensitivity, specificity, positive and negative predictive values, and false-negative rate of the technique.

MATERIALS AND METHODS

Study Design

This cross-sectional study was conducted to evaluate the performance of SLNB using MBD in early breast cancer patients.

Study Setting and Period

The study was carried out in the In-Patient Department of General Surgery and Surgical Oncology at SIMS&RC, a tertiary care center in India. Data collection occurred from June 2023 to September 2024.

Sample Size

A total of 40 patients were enrolled based on feasibility and prior studies indicating sufficient statistical power for detecting SLNB efficacy with this sample size [10].

Inclusion Criteria

Patients aged 18 years and older with histologically confirmed T1 or T2 breast tumors were included. Only those with clinically and radiologically negative axillary lymph nodes (N0) were eligible.

Exclusion Criteria

Patients with a history of prior axillary surgery or breast radiotherapy were excluded due to potential alterations in lymphatic drainage patterns [3].

Procedure

SLNB was performed under general anesthesia. A 1% MBD solution was prepared, and 2–5 mL was injected peritumorally or subareolarly, depending on tumor location. After 5–10 minutes, a small incision was made in the axilla to identify blue-stained lymph nodes. Identified SLNs were excised and sent for frozen section analysis intraoperatively, followed by histopathological examination (HPE) using hematoxylin and eosin staining. ALND was performed if the SLN was positive on frozen section or if no SLN was identified.

Outcome Measures

The primary outcomes included the identification rate (percentage of cases where SLN was identified), accuracy (concordance between SLN and axillary status), sensitivity (ability to detect true positives), specificity (ability to detect true negatives), positive predictive value predictive value (PPV), negative predictive value (NPV), and false-negative rate (FNR).

Statistical Analysis
Descriptive statistics were used to summarize patient demographics and tumor characteristics. Diagnostic performance metrics were calculated using standard formulas based on HPE results as the gold standard.

Ethical Considerations
The study was approved by the SIMS&RC Institutional Ethics Committee. Informed consent was obtained from all participants.

RESULTS
A total of 40 patients, aged 35–70 years (mean age: 52.3 ± 9.8 years), were included. Tumor locations included the upper outer quadrant (80%), lower outer quadrant (15%), lower inner quadrant (3%), and tail of Spence (2%). Right-sided tumors were observed in 20% and left-sided in 80%. Mastectomy was performed in 34 patients (85%), while 6 (15%) underwent breast-conservative surgery (BCS).

Table 1: Patient and Tumor Characteristics

Variable	Number (%) or Mean ± SD
Age (years)	52.3 ± 9.8
Tumor Location	
Upper Outer Quadrant	32 (80%)
Lower Outer Quadrant	6 (15%)
Lower Inner Quadrant	1 (3%)
Tail of Spence	1 (2%)
Side	
Right	8 (20%)
Left	32 (80%)
Surgery Type	
Mastectomy	34 (85%)
BCS	6 (15%)

Table 2: Surgical Outcomes

Surgery Type	Number (%)	SLN Positive (HPE)	SLN Negative (HPE)
Mastectomy	34 (85%)	13 (38.2%)	21 (61.8%)
BCS	6 (15%)	2 (33.3%)	4 (66.7%)

Table 3: SLNB Performance Metrics

Metric	Value
Identification Rate	40/40 (100%)
Accuracy	36/38 (94.73%)
Sensitivity	15/16 (93.75%)
Specificity	22/22 (100%)
PPV	15/15 (100%)

Metric	Value
NPV	22/23 (75%)
FNR	1/16 (6.25%)

Table 4: Histopathological Findings

Finding	Number (%)
SLN Positive (HPE)	15 (37.5%)
SLN Negative (HPE)	25 (62.5%)
ALN Positive (HPE)	1 (2.5%)
Frozen Section Positive	21 (52.5%)

Table 5: Discoloration Outcomes

Discoloration	Number (%)
Present	19 (47.5%)
Absent	21 (52.5%)

The SLN was identified in all 40 cases (identification rate: 100%). Of the 38 patients with complete ALND data, the accuracy was 94.73% (36/38). Sensitivity was 93.75% (15/16), reflecting one false-negative case where the SLN was negative but ALN was positive on HPE. Specificity was 100% (22/22), with no false positives. The PPV was 100% (15/15), and the NPV was 75% (22/23). The FNR was 6.25% (1/16). Discoloration from MBD was observed in 19 patients (47.5%).

DISCUSSION

This study demonstrated that SLNB using MBD alone is a highly effective technique for axillary staging in early breast cancer, with an identification rate of 100% and an accuracy of 94.73%. These findings align with prior research. Gupta et al. reported a 96.7% identification rate using MBD alone in a randomized trial, with no significant difference compared to combined MBD and radioisotope techniques ($p = 0.67$) [10]. Similarly, Hermansyah et al. found a 95.8% identification rate with MBD, reinforcing its reliability [11].

The sensitivity of 93.75% and specificity of 100% in our study compare favorably to the NSABP B-32 trial's dual-technique results (sensitivity: 90.9%, specificity: 100%) [6]. However, our FNR of 6.25% is lower than the 9.8% reported in NSABP B-32, suggesting that MBD alone may suffice in resource-limited settings. Brahma et al. reported an FNR of 5.9% with MBD, consistent with our findings ($p > 0.05$ when compared informally) [5]. The single false-negative case in our cohort highlights the importance of meticulous surgical technique and histopathological confirmation, as noted by Martinez-Ramos et al. [14].

Compared to studies using radioisotopes, our PPV (100%) and NPV (75%) indicate robust predictive accuracy, though the NPV is lower than some dual-technique studies (e.g., 88.6% in NSABP B-32) [6]. This may reflect our smaller sample size or tumor heterogeneity. Eldrageely et al. found no significant difference between MBD and isosulfan blue ($p = 0.82$), supporting MBD's equivalence to other dyes [8].

The high mastectomy rate (85%) in our cohort contrasts with Western trends favoring BCS (e.g., 60–70% in the US) [1], likely due to patient preference or advanced presentation in India [13]. Discoloration in 47.5% of patients was transient and aligns with MBD's known safety profile [9].

Our results support MBD's utility in non-metropolitan areas, where radioisotopes are scarce [7]. However, the single-center design and modest sample size limit generalizability, necessitating multicenter validation.

CONCLUSION

The MBD injection technique for SLNB in early breast cancer demonstrated excellent efficacy, with a 100% identification rate, 94.73% accuracy, and a low FNR of 6.25%. Its high sensitivity, specificity, and predictive values affirm its reliability as a standalone method, particularly in resource-constrained settings. These findings advocate for its broader adoption to reduce ALND-related morbidity while maintaining oncological safety. Future studies should explore larger, multicenter cohorts to confirm these outcomes and refine the technique's application.

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