REVIEW ARTICLE

Use of methylene blue in axillary sentinel lymph node biopsy in limited resource settings: A narrative review

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Abstract

Background: Sentinel lymph node biopsy (SLNB) is a standard technique for axillary staging in early breast cancer with clinically node-negative axillae. Radioactive tracer or Isosulfan Blue are the accepted methods of detecting sentinel nodes. Methylene blue (MB) dye has emerged as an accessible and cost-effective alternative to radioisotope tracers, particularly in low- and middle-income countries (LMICs).

Objectives: To review the use of MB and assess its efficacy, diagnostic accuracy, safety, and practical considerations in SLNB, particularly in LMIC settings. As a secondary objective, to compare the efficacy of MB with other tracer dyes.

Methods: A literature review was conducted using PubMed and Google Scholar databases. Studies evaluating MB in SLNB, published between 2000 and 2024, were included. Key outcomes included identification rate, false-negative rate (FNR), and adverse events. Data were synthesized narratively and tabulated.

Results and discussion: Among 16 eligible studies, MB demonstrated identification rates between 78 to 98%, with FNRs ranging from 3 to 10%. MB was shown to be safe, with minor adverse effects including dermal tattooing and rare allergic reactions. Its low cost and ease of availability make it more suitable for use in LMICs.

Conclusion: MB is a viable and effective tracer for SLNB in breast cancer, especially in resource-constrained settings. Adoption into local protocols and further comparative studies are recommended.

Keywords: Methylene blue, sentinel lymph node biopsy, breast cancer, and blue dye tracer

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Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide, as well as in Sri Lanka. It accounts for approximately 2.3 million new cases annually in the world (WHO 2022) and around 5,500 new cases in Sri Lanka. Axillary lymph node status remains one of the most significant prognostic indicators in breast cancer, and SLNB has replaced the more invasive axillary lymph node dissection (ALND) in patients with clinically node-negative axillae, substantially reducing surgical morbidity. [1-3]

Traditionally, SLNB uses a radioisotope such as Technetium-99m and a blue dye (commonly isosulfan blue or patent blue V) to localise the sentinel lymph node (SLN). However, limitations such as high costs, allergic reactions, regulatory constraints, and the need for nuclear medicine infrastructure restrict the universal adoption of this dual-tracer method.[4] Consequently, MB has gained attention as a viable alternative, especially in LMICs where resources are limited.[5,6] The review explores the mechanism, clinical efficacy, diagnostic accuracy, comparative benefits, limitations, best practices, and future trends in using MB for SLNB in breast cancer.

Methods

Databases searched included PubMed and Google Scholar. Keywords used were "methylene blue," "sentinel lymph node biopsy," "breast cancer," and "blue dye tracer." The search included studies published from January 2000 to April 2024.

Studies published in English-language journals evaluating MB in SLNB for breast cancer, reporting identification rate, FNR, or safety profile, were included. Case reports, non-human studies, and review articles without original data were excluded.

The data related to study design, study population, MB technique, identification rate, FNR, and complications were extracted. Discrepancies were resolved by consensus. Narrative synthesis and summary tables were used.

A total of 312 records were identified through database searches (PubMed and Google Scholar). After systematic exclusion, only 16 studies were eligible and included in this analysis.

Results

A total of 16 studies met the inclusion criteria, including randomized controlled trials, systematic reviews, prospective cohorts, and retrospective analyses from various global regions, especially LMICs.

Diagnostic Accuracy

- Identification rates: 78-98% [6-20]
- FNR: 3-10% [6-20]
- Pooled analysis showed comparable efficacy with dual-tracer methods in many settings[6-20]

Adverse Effects (Table 1)

MB is generally well tolerated. Reported complications include:

- Dermal tattooing (persistent blue skin staining)
- Minor allergic reactions
- Local tissue necrosis (rare)

Comparison with Other Tracers

Compared to Tc99 radioisotopes:

- MB has slightly lower identification rates.
- Benefits include lower cost, with no nuclear licensing required.

Table 1. Summary of adverse events associated with methylene blue

Adverse Event	*Frequency*	*Severity*	*Notes*
Dermal tattooing	Common	Mild	Can persist for weeks to months[20]
Allergic reactions	Rare	Mild to moderate	Usually, mild skin reactions[20]
Local tissue necrosis	Very rare	Severe	Requires surgical management, if any[20]
Pain at injection site	Occasional	Mild	Usually, self-limiting [20]

Compared to other dyes:

- Isosulfan blue and patent blue carry a higher risk of allergy[20].
- MB is superior in accessibility and safety.[20]

Discussion

Mechanism of action of MB and application

MB is a synthetic dye in the thiazine class, known for its deep blue colour. When injected intradermally, subdermally, or subareolarly near the tumour or areolar complex, MB migrates through the lymphatic vascular system to the sentinel node, staining it blue for visual identification.[5,6]

The optimal volume and concentration of MB vary from surgeon to surgeon, but common practice involves injecting 1-2 ml of (0.5%-1%) MB solution.[7] The node is typically visualised within 10 to 15 minutes post-injection, and dissection is guided by direct visualisation of the stained lymphatic channel and node.[5,8,9]

Efficacy and diagnostic performance

Numerous studies have examined the use of MB as a single-agent tracer in SLNB. In a meta-analysis of 18 studies comprising 1,559 patients, pooled data reported a sentinel node identification rate of 91%, a sensitivity of 87%, and an accuracy of 94%.[10] While MB alone exhibits slightly lower efficacy compared to dual-tracer techniques (95%), its diagnostic performance is generally within acceptable clinical thresholds.[10]

In a prospective Indian study involving 329 patients, the sentinel identification rate was 96.6% with a false-negative rate (FNR) of 8% using MB alone.[8] These results highlight the feasibility and reliability of MB in appropriately selected patient populations.

Comparison with other tracers

Structurally, MB is a smaller molecule compared to other molecules used for sentinel node biopsy[6] (Figure 1). One criticism of MB is that it may pass to the second tier of nodes by the time the surgeon detects the sentinel node. As a result, the surgeon may mistakenly biopsy the second-tier node as the sentinel node.[5,6,9] However, MB has been compared with other dyes and dual-tracer techniques across various studies.[8,11] In a randomised controlled trial comparing MB with isosulfan blue, no statistically significant differences in sentinel node detection rate were shown.[12]

Dual-tracer techniques consistently demonstrate higher identification rates (95-98%) and lower FNRs (~5%). However, in LMICs, the logistical and economic challenges of using radioisotopes make MB a practical alternative. A network meta-analysis in 2021 indicated that MB combined with another tracer, such as indocyanine green (ICG), improves detection rates (96% to 97%) while maintaining safety.[13]

Practical considerations in LMICs

MB is particularly advantageous in LMICs due to its affordability, ease of use, and non-reliance on specialised equipment. Several studies done in Asian countries have documented the practical benefits of MB in LMIC settings and its widespread use due to low cost and satisfactory identification rates.[14-17] Similarly, its effectiveness is demonstrated in hospitals lacking nuclear medicine facilities.[14] These findings are echoed in reports from African nations where MB has enabled SLNB adoption in rural and peripheral centres.[18] It is understood that in LMICs of South Asia, South-East Asia, and parts of Africa, MB is widely used in public and private hospitals and training centres for sentinel node biopsy.

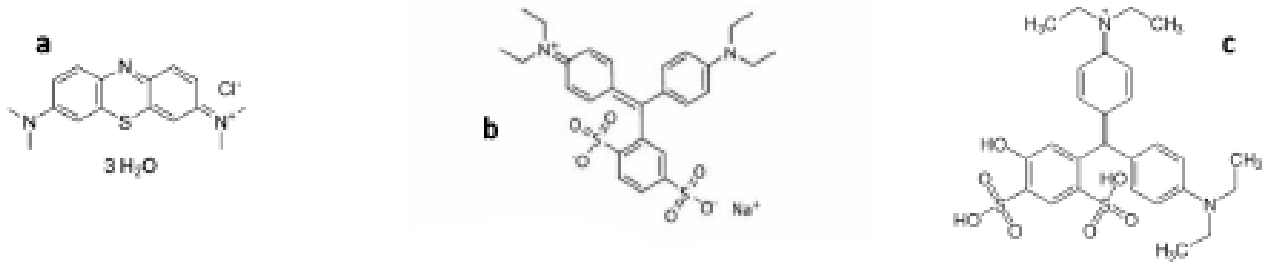

Figure 1. Molecular structure of commonly used dyes (a) Methylene blue, (b) Isosulfan blue and (c) Patent Blue V (Sulphan Blue).

Cost effectiveness

MB is considerably less expensive than isosulfan blue and does not require nuclear medicine facilities.[11] The cost of MB is a fraction of that of isosulfan blue. It obviates the need for expensive gamma probes and nuclear medicine departments, making it an economically viable tracer for SLNB in LMICs. The incremental cost of isosulfan blue is $108.29/case (SD+/-$43.4) in the USA. These studies highlight that the reduced infrastructure requirements further contribute to cost savings and broader implementation in resource-constrained settings.[19]

Safety profile

Lower incidence of anaphylaxis was reported with MB compared to other dyes.[15,20]

Training and accessibility

Use of MB simplifies the learning curve for surgeons and allows broader implementation in decentralised healthcare settings. Moreover, the lack of dependence on radioactive substances ensures that MB can be used even in rural and peripheral health institutions, making SLNB a feasible procedure outside urban tertiary care centres.[10,21]

Integration into healthcare policies

Some LMICs are exploring the development of standardised protocols that favour MB due to its ease of logistics and widespread availability.[22]

Limitations and adverse events of MB (Table 1)

Despite its many advantages, MB is not without drawbacks.

- **False negatives:** The FNR of MB alone is marginally higher than dual-tracer methods, requiring careful patient selection.[17,20,21]
- **Local tissue reactions:** Cases of skin necrosis and ulceration have been reported, particularly with high concentrations or improper injection techniques.[8,20]
- **Tattooing:** Persistent blue discolouration of the skin may occur, which could be a cosmetic concern, especially in fair-skinned individuals.[20]
- **Systemic side effects:** Rare cases of serotonin syndrome, especially in patients on serotonergic medications such as SSRIs, have been noted. Clinicians should perform thorough drug histories before the use of MB.[2,10,20]

Recommendations and best practices (Table 2)

- **Use a concentration of 0.5% MB, when feasible:** 0.5% concentration of MB is effective for SLNB, providing a balance between adequate lymphatic uptake and minimising adverse reactions.[7]
- **Preference for subareolar over peritumoral injection to reduce tissue necrosis:** Subareolar injection of MB resulted in a higher sentinel lymph node identification rate compared to peritumoral injection, with no significant difference in false-negative rates.[4,7]
- **Gentle, slow injection with fine-gauge needles:** The American College of Surgeons Oncology Group Z0010 study reported that careful injection techniques, including the use of fine-gauge needles, are essential to minimise complications such as skin necrosis and to ensure accurate lymphatic mapping.[20]
- **Post-injection massage to enhance lymphatic uptake and reduce local pooling:** It is recommended to perform a 4-minute post-injection massage to facilitate the movement of MB through the lymphatic system, thereby improving sentinel lymph node identification. [7,23]
- **Use of prophylactic anti-allergic measures in patients with atopy:** Though methylene blue has a lower incidence of allergic reactions compared to isosulfan blue, it is prudent to administer prophylactic anti-allergic medications in patients with known allergies to minimise the risk of adverse reactions.[20]

Table 2. Practice recommendations for MB

Practice	*Rationale*
Use 1% MB dye	Effective visualization of SLNs [13,14]
Inject peri-areolar or subdermal	Better lymphatic uptake [18]
Massage the site for 5-10 min	Promotes tracer migration [19]
SLN dissection within 10-20 min	Prevents diffusion and fading [21]

Innovations and future directions

Emerging techniques aim to enhance the accuracy and safety of SLNB while leveraging MB's accessibility. Combining MB with ICG allows for fluorescence-guided SLNB, improving visualisation.[24] AI-assisted surgery is a recent advancement in sentinel node biopsy. Research into artificial intelligence and augmented reality systems for SLN localisation is ongoing.[25]

Some LMICs, including Sri Lanka, are incorporating MB-based SLNB protocols into national breast cancer management guidelines.

Conclusion

Methylene blue is an effective and economical alternative for SLNB in breast cancer, especially in resource-constrained settings. Although dual-tracer techniques remain the gold standard, MB offers an acceptable compromise in terms of efficacy, accuracy, safety, and accessibility. Continued improvement of techniques, surgeon training, and integration with other technologies, such as ICG and AI, will further enhance the role of MB in sentinel node biopsy for breast cancer surgery.

Authors' Contributions

Concept and design, literature review, compilation and critical analysis of manuscript, manuscript editing and proofreading: RP.

References

1. N Krag UD, Anderson SJ, Julian TB, Brown ScD AM, Harlow SP, Costantino DrPH JP, et al. National Surgical Adjuvant Breast and Bowel Project Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Articles Lancet Oncol* [Internet]. 2010; **11**: 927-60. Available from: www.thelancet.com/oncology. doi: 10.1016/S1470-2045(10)70207-2

8. Varghese P, Mostafa A, Abdel-Rahman AT, Akberali S, Gattuso J, Canizales A, et al. Methylene blue dye versus combined dye-radioactive tracer technique for sentinel lymph node localisation in early breast cancer. *European Journal of Surgical Oncology.* 2007; **33**(2): 147-52. doi: 10.1016/j.ejso.2006.09.026

9. Khadka S, Suresh J, Prem A, Mishra P, Kataria K, Dhar A, et al. Sentinel node mapping in early breast cancer: A randomized comparison of fluorescein guided all india institute of medical sciences, anurag's technique with technetium-99 m sulfur colloid plus methylene blue. *Indian Journal of Nuclear Medicine.* 2022 Jul 1;37(3):236-44. doi: 10.4103/ijnm.ijnm_3_22

10. Li J, Chen X, Qi M, Li Y. Sentinel lymph node biopsy mapped with methylene blue dye alone in patients with breast cancer: A systematic review and metaanalysis. *PLoS One.* 2018; **13**(9). doi: 10.1371/journal.pone.0204364

11. Blessing WD, Stolier AJ, Teng SC, Bolton JS, Fuhrman GM. A comparison of methylene blue and lymphazurin in breast cancer sentinel node mapping [Internet]. 2002 https://www.americanjournalofsurgery.com/article/S0002-9610(02)00948-0/fulltext. doi: 10.1016/s0002-9610(02)00948-0

12. Gupta V, Raju K, Rao TS, Naidu CK, Goel V, Hariharan N, et al. A Randomized Trial Comparing the Efficacy of Methylene Blue Dye Alone Versus Combination of Methylene Blue Dye and Radioactive Sulfur Colloid in Sentinel Lymph Node Biopsy for Early Stage Breast Cancer Patients. *Indian J Surg Oncol.* 2020; **11**(2):216-22. doi: 10.1007/s13193-019-01023-3

13. Liu HJ, Sun MS, Liu LY, Yu ZH, Chen XX, Liu Q, et al. The detection rate of methylene blue combined with another tracer in sentinel lymph node biopsy of early-stage breast cancer: a systematic review and network meta-analysis. *Transl Cancer Res.* 2021; **10**(12): 5222-37. doi: 10.21037/tcr-21-1239

14. Nandu VV, Chaudhari MS. Efficacy of Sentinel Lymph Node Biopsy in Detecting Axillary Metastasis in Breast Cancer Using Methylene Blue. *Indian J Surg Oncol.* 2017; **8**(2):109-12. doi: 10.1007/s13193-016-0616-z

15. Gupta V, Raju K, Rao TS, Naidu CK, Goel V, Hariharan N, et al. A Randomized Trial Comparing the Efficacy of Methylene Blue Dye Alone Versus Combination of Methylene Blue Dye and Radioactive Sulfur Colloid in Sentinel Lymph Node Biopsy for Early-Stage Breast Cancer Patients. *Indian J Surg Oncol.* 2020; **11**(2): 216-22. doi: 10.1007/s13193-019-01023-3

16. Hermansyah D, Rahayu Y, Azrah A, Pricilia G, Paramita D, Siregar ES, et al. Accuracy Of Methylene Blue Test As Single Technique For Sentinel Lymph Node Biopsy In Early Stages Breast Cancer. *Asian Pacific Journal of Cancer Prevention.* 2021; **22**(9): 2765-9. doi: 10.31557/APJCP.2021.22.9.2765

17. Aimir M, Nasser A, Rokayah J, Hardin M, Sohail M. The sensitivity and specificity of methylene blue dye as a single agent in sentinel lymph node biopsy for early breast cancer. *Med J Malaysia.* 2022; **77**(5): 552-7.

18. Okoye CL, Ezeome ER. Use of methylene blue dye for lymphatic basin mapping and sentinel lymph node biopsy in breast cancer patients in Enugu, Nigeria. *Niger J Clin Pract.* 2022; **25**(11): 1805-11. doi: 10.4103/njcp.njcp_154_22

19. Das G, Kodali R, Khanna S, Purkayastha J, Talukdar A, Kakoti L. Sentinel Lymph Node Biopsy Using a Single-Dye Technique in a Cancer Center of North-East India. *South Asian J Cancer.* 2021; **10**(2): 69-71. doi: 10.1055/s-0041-1733350

20. Thevarajah S, Huston TL, Simmons RM. A comparison of the adverse reactions associated with isosulfan blue versus methylene blue dye in sentinel lymph node biopsy for breast cancer. *Am J Surg*. 2005; **189**(2): 236-9. doi: 10.1016/j.amjsurg.2004.06.042

21. Xu YL, Liu XJ, Zhu Y, Lu H. Preoperative localization of sentinel lymph nodes using percutaneous contrast-enhanced ultrasonography in patients with breast cancer. *Gland Surg*. 2022; **11**(2): 369-77. doi: 10.21037/gs-22-10

22. National guidelines for the management of early and locally advanced breast cancer in Sri Lanka 2021 National Cancer Control Programme Ministry of Health [Internet]. Available from: https://www.nccp.health.gov.lk/

23. Liu HJ, Sun MS, Liu LY, Yu ZH, Chen XX, Liu Q, et al. The detection rate of methylene blue combined with another tracer in sentinel lymph node biopsy of early-stage breast cancer: a systematic review and network meta-analysis. *Transl Cancer Res*. 2021; **10**(12): 5222-37. doi: 10.21037/tcr-21-1239

24. Yang Q hui, Zhang X jian. Indocyanine green combined with methylene blue versus methylene blue alone for sentinel lymph node biopsy in breast cancer: a retrospective study. *BMC Surg*. 2023; **23**(1). doi: 10.1186/s12893-023-02037-z

25. Zhu T, Huang YH, Li W, Zhang YM, Lin YY, Cheng MY, et al. Multifactor artificial intelligence model assists axillary lymph node surgery in breast cancer after neoadjuvant chemotherapy: multicenter retrospective cohort study. *Int J Surg*. 20231; **109**(11): 3383-94. doi: 10.1097/JS9.0000000000000621