

Methylene Blue Dye for Sentinel Lymph Node Biopsy in Breast Cancer: Our Experience

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Abstract

Context: Evaluation of sentinel lymph node is essential in deciding on need for axillary clearance in patients with breast cancer. We evaluate the role of methylene blue dye in identifying sentinel lymph node in our institution. *Aims:* To evaluate the use of methylene blue dye to detect axillary lymph node involvement in breast carcinoma. *Settings and Design:* Prospective interventional study. *Methods and Material:* Women with node negative, biopsy proven breast carcinoma scheduled for modified radical mastectomy or breast conservative surgery were selected. Consent was taken. Five ml of 2% methylene blue dye was injected to the lateral aspect of tumor and massaged for five minutes. Axillary dissection was done. Lymph nodes stained blue and unstained were collected and examined separately for tumor involvement. Patient was examined postoperatively to evaluate for any adverse reactions. *Statistical analysis used:* Using Chi-square test- Fisher's Exact Test. *Results:* Our study showed that the probability of sentinel node representing axillary status was significant (p value - 0.022). Sentinel and non-sentinel histology were in agreement in 80% cases. *Conclusions:* Methylene blue dye is an effective and safe blue dye for sentinel lymph node biopsy.

Keywords: Methylene Blue Dye; Breast Cancer; Sentinel Lymph Node.

Introduction

Breast cancer was the most common malignancy worldwide in the year 2012 [1]. Though, 70%-80% of breast cancer patients do not have lymph node metastasis at the time of diagnosis [2], presence of a nodal metastasis in breast cancer significantly decreases the 5-year survival rate [3]. Hence, it is important to accurately identify cases with nodal metastasis in midst of patients without nodal metastasis. The initial node to which lymph of the breast drains is called as sentinel lymph node (SLN). Identification of tumor deposits in this node helps us decide over the need of complete axillary dissection.

Sentinel lymph nodes are usually identified by injecting a dye or a radiotracer into the tissue surrounding tumor and identifying the first lymph node to take-up the dye. The lymph nodes are then subjected to frozen section. If found to have tumor deposits, a complete axillary dissection is performed. Various dyes have been used for this purpose. Few examples include isosulphan blue, patent V and methylene blue dye (MBD). A dye which is cost-effective, produces least allergy reactions including skin rashes, but effectively identifies the SLN is ideal for this purpose.

In our institution, sentinel lymph node biopsy (SNLB) is not performed routinely. The high costs and irregularity of obtaining samples were the main factors why we refrained from using isosulphan blue dye and radiotracer as detection methods. Methylene blue was relatively inexpensive. However, it was known to cause anaphylaxis and skin rash with staining, hence there was apprehension for its widespread use. With reassuring literature over the years, affirming its safety and efficacy, we planned a

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study to evaluate the use of MBD in clinically node negative histologically proven breast carcinoma.

Methods

Study Population

We conducted a prospective interventional study in our hospital. We included women with established diagnosis of carcinoma breast planned to undergo modified radical mastectomy (MRM) or breast conservative surgery (BCS) and without clinically palpable axillary lymph nodes (ALN). Thirty five sequentially available eligible patients were included in the study. Approval for this study was obtained from Institutional Ethical Committee. Informed consent was taken from participants. Male breast cancer patients, patients with multifocal tumors, or with a history of allergy or proven carcinoma breast with prior history of incision or excision biopsies for the breast lump were excluded.

Identification of Sentinel Lymph Node

The patient demographic details were recorded. The SLN was identified by MBD injection. After administering general anaesthesia, painting and draping for the operation, five ml of a 2% solution was injected on the lateral aspect of the tumor, into the breast parenchyma. This was done through the portion of the skin which was planned for excision. The injection site was massaged for five minutes. In MRM, the SLN was retrieved after raising superior flap. All blue stained nodes receiving a blue lymphatic channel were identified as SLN. In BCS, after injecting the dye, axillary incision was made and the nodes that stained blue were dissected out and retrieved. Mastectomy or wide local excision of breast lump was performed as scheduled. For both MRM and BCS, the axillary lymph node dissection (ALND) was completed according to the routine set procedure. Breast specimen, the blue stained lymph nodes and the unstained lymph nodes were examined separately by the pathologist.

Sample Size

To prime the surgeons with the required technique for the sentinel lymph node biopsy, the procedure was done initially on patients scheduled for routine MRM irrespective of nodal status. This procedure was followed for the first 10 cases so that all operating surgeons were familiar and confident with the new technique. The results of these 10 cases were not included in the statistical analysis. The procedure was then done on 25 clinically node negative, biopsy proven breast carcinoma patients as per the protocol.

Intra operative findings were documented and immediate postoperative condition was evaluated.

Statistical Analysis

Statistical significance was determined using the Chi-square tests- Fisher's Exact Test ($p < 0.05$). Sensitivity and negative predictive values were calculated and analysed. Sentinel lymph node is defined as the first lymph node in the axilla to be involved in the metastatic process. Hence detection of tumour in the sentinel lymph node and absence of spread in the complete dissection specimen is acceptable as the natural course of the disease. Therefore, it cannot be defined as false positive and was not calculated. Specificity and positive predictive values which are derived from false positive value were not calculated for this study.

Results

The age of the patients ranged from 39 to 64 years with mean age of 52.7 years. Twenty (80%) patients were in the post-menopausal group and five (20%) patients were in the pre-menopausal group. Out of 25 patients 14 (56%) presented with left sided carcinoma and in 11 (44%) patients, it was on the right side. Twelve out of 25 (48%) suffered from the tumour in upper outer quadrant. Twenty three patients underwent MRM and two patients underwent BCS. In level I axillary dissection, sentinel lymph node could be clearly identified in 20 (80%) patients. A single lymph node was blue stained in 14 (56%) patients and there were two lymph nodes coloured blue in six patients (24%). The average size of sentinel lymph node was 1.46×0.82 cm.

Average number of axillary nodes that did not have blue dye per case was 10.52. On histopathology, tumor positive ALN average per case was 11 and that of tumor negative axillary lymph nodes was 14.

The twenty patients whose axillary dissection revealed blue dye were evaluated further regarding the histopathological status of the lymph nodes (stained i.e. SLN and unstained i.e. ALN). In seven, tumour invasion was seen in both sentinel and axillary lymph nodes and in nine, tumour was seen in neither. In two patients, tumor deposits were seen in SLN but not in ALN. This indicates that SLN is involved by tumor prior to involvement of ALN. However, in two patients, though the SLN were negative for tumour invasion, the ALN were positive for malignancy on histopathology. Postoperatively, two patients had bluish discolouration of drain fluid which cleared within two days without any other discomfort to the patient. Skin discolouration was not seen in any of the cases as the portion of skin containing the site of dye injection was already excised during the operation.

Sentinel lymph node representing axillary status was statistically significant ($p = 0.022$) when assessed by Chi-square tests- Fisher's Exact Test. Sensitivity was 77.7%. The study had a false negative value of 22.2% and negative predictive value of 81.8%.

Discussion

Modified radical mastectomy is a routinely done procedure for patients diagnosed with breast malignancy. It involves removal of breast tissue along with its lymph nodes in the axilla. As a consequence, post-operative upper limb edema, pain and numbness can result. Rarely, limitation of shoulder movements, vascular and neuronal injuries may also occur [4]. Patients with breast cancer are now presenting in earlier stages, with less population having clinical involvement of the ALN. Identification of SLN add value in the management of these patients. Sentinel lymph node biopsy is therefore performed to evaluate the metastatic status of the axilla. If SLN is found to be free of tumor, avoiding further axillary dissection has become the standard of care [5]. Thus, a properly performed SLNB identifies patients who need further axillary clearance, while sparing others a potentially morbid ALND [6].

Sentinel lymph nodes can be detected by two methods. A dye is injected lateral to the tumor in the breast and the axilla is visualized to recognize any blue stained lymph nodes. Isosulphane blue and MBD have been used previously [7]. Radioactive tracer can also be used. Sentinel lymph nodes are then detected using a gamma probe. These two methods have also been used in combination [8]. Varghese et al. compared the accuracy and success rate of MBD alone versus combined MBD and radioactive colloid for localizing sentinel lymph node in early breast cancer. They concluded that the combined technique facilitates quicker identification of sentinel lymph node. However, the dye alone can be used successfully in centers without nuclear medicine facilities [9]. Methylene blue is cheaper and is easily available. However, skin necrosis and staining have been noted with its usage [10].

Few other studies have documented serious side-effects for the use of MBD. N Piscatelli, et al. documented a 7% rate of fat necrosis at the site of injection with MBD [11]. Though many studies have reported allergic reactions to the usage of MBD [12-14]. It is still considered the safest among the blue dyes being used in sentinel node mapping [15]. In our study, none of the 35 patients who were injected with MBD showed any allergic reaction.

Altan Özdemir et al. noted that SLN detection rate of 90% or more and false-negative rate of 5% or less indicated that only SLNB without axillary dissection can be performed. Nandu et al performed a similar

study on 35 node negative, biopsy proven malignancy of the breast. They injected MBD by intra-lesional and peri-lesional route 20 minutes prior to surgery. Their results showed that sensitivity of SLNB is 90.48%, specificity is 85.71%, PPV of is 90.48%, NPV is 85.71%, and accuracy is 88.57%. They concluded that SLNB is an effective method of staging the axilla and deciding on axillary clearance in patients of carcinoma breast [16]. In our study, we detected 80% of SLN by injection of dye in the peri-lesional area and a negative predictive value was 81.8%. We attribute the lower detection rate to the learning curve involved in the technique. Therefore, we feel that MBD injection is a good option for detection of SLN in case of node negative breast cancer.

Conclusion

Methylene blue dye is an effective and safe blue dye to detect sentinel lymph node in a clinically node negative breast cancer.

Key Messages

Use of methylene blue dye is effective in detecting sentinel lymph node to decide on the requirement of axillary clearance.

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