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Sentinel Lymph Node Biopsy Using Methylene Blue Dye - The Vicente Sotto Memorial Medical Center Experience

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Objective: To determine the accuracy of SLNB using methylene blue dye.

Methods: Breast cancer patients consulting at the VSMMC Breast Center with biopsy proven adenocarcinoma of the breast, a Tis, T1, T2 or T3 primary breast tumor and clinically negative ipsilateral axilla by palpation and ultrasound, were included in the study. The subjects underwent either modified radical mastectomy or breast conservation therapy. Subareolar injection of 5 ml 1% methylene blue dye 5 minutes prior to sentinel lymph node biopsy. Three blue staining axillary lymph nodes were taken and sent to pathology for frozen section evaluation and after surgery, H & E staining. A completion axillary lymph node dissection was done in all patients. Accuracy of SLNB using methylene blue was calculated using final histopathology results as gold standard.

Results: Twenty patients were included in this study. SLNB in this group had an accuracy, sensitivity, specificity, PPV, and NPV of 95.0%, 83.3%, 100%, 100%, and 93.3%, respectively. The false negative rate is 6.7%. On the average, the SLNs were identified in 14 minutes.

Conclusion: Sentinel lymph node dissection with methylene blue has an accuracy of 95% in the VSMMC Breast Center.

Key words: sentinel lymph node biopsy, methylene blue dye, breast cancer

For nearly a century, the standard of surgery for breast cancer in the Philippines includes an axillary lymph node dissection. Complications of axillary dissection include pain, paresthesia, seroma, infection, limitation of shoulder motion, and lymphedema. The long-term consequences of axillary dissection on quality of life can be substantial, even among those who have apparently normal post-operative recovery. Lymphedema, which occurs in 6% to 30% of patients after axillary dissection is a particularly troubling lifelong problem for which there is no curative therapy.[1,2]

Sentinel lymph node biopsy is a minimally invasive method of assessing the axilla and is considered an important option in breast cancer management in other countries. This approach lessens the sequelae of standard axillary dissection. Sentinel lymph node identification uses various agents such as radioactive colloid, methylene blue dye, and isosulfan blue dye. Methylene blue dye as a cheaper alternative compared to other dyes for SLNB could have cost-saving potentials in developing countries.

Although numerous studies have demonstrated that SLNB can accurately determine the axillary nodal status, the sensitivity of the procedure for detection of nodal metastases has been variable. The most critical factor is the false-negative rate (the proportion of patients with axillary nodal metastases who are found, incorrectly, to have histologically negative SLNs). Although it has been suggested that a false-negative rate of less than 5% is acceptable, previous studies reported false-negative rates ranging from 0% to 29% averaging 7.3% overall.[2] Due to the variable false-negative rates and the fact that most of the published studies involved institutions and individuals specializing in breast cancer, there has been skepticism about the ability to disseminate this technology into widespread surgical practice.

The American Society of Breast Surgeons recommends that a sentinel lymph node identification rate of at least 85 percent with a false-negative rate of 5 percent or less is required in order to abandon axillary dissection. The Society also recommends that

a minimum of 20 sentinel lymph node biopsy cases should be performed with axillary dissection in order to minimize the risk of false negative results.[3,4]

The acceptable sentinel lymph node identification and false-negative rate associated with the methylene blue dye injection technique may indicate that this procedure is a suitable alternative to routine axillary dissection across a spectrum of surgical practice. By applying this concept to breast cancer, most patients can be spared the morbidity of axillary dissection, which may not be necessary in patients with clinically negative axilla.[4]

This study was undertaken to determine the accuracy of sentinel lymph node biopsy using methylene blue dye in predicting nodal metastases in Vicente Sotto Memorial Medical Center (VSMMC) Breast Center.

Methods

The research protocol was approved by the Research Ethics Committee of VSMMC. All female patients with breast cancer consulting at the Breast Clinic of Vicente Sotto Memorial Medical Center from October 5, 2009 to November 5, 2010 were assessed for eligibility. Informed consent was obtained from all the participating patients. Inclusive criteria for SLNB using methylene blue dye are biopsy proven adenocarcinoma of the breast, a Tis, T1, T2, T3 primary breast tumor and clinically negative ipsilateral axilla by palpation. Exclusion criteria include tumors with skin involvement, clinically palpable axillary lymph nodes, previous axillary surgery, no residual tumor after biopsy, and preoperative chemotherapy or radiotherapy. The operative site was prepared aseptically and sterile drapes were applied. A total of 5ml sterile aqueous 1% methylene blue dye for injection was injected into the subareolar tissue.[2,3] A gauge 23 needle in a 5ml syringe was used with moderate pressure applied during introduction of the dye. The breast was massaged for 5 minutes prior to incision. The surgeon approached directly the SLN via an axillary incision if breast conserving surgery is the proposed definitive procedure.[3] If mastectomy is the definitive procedure, the surgeon goes for the SLN after creating the superior flap. All blue nodes receiving a blue lymphatic channel are sentinel nodes. The number of nodes to be taken for biopsy was noted and should not exceed 3, otherwise the benefits of the limited dissection required for SLNB could be compromised. The duration of axillary dissection until the sentinel lymph node is identified was recorded. The nodes taken will be sent to the pathologist for frozen section biopsy and eventually for H & E staining. A completion axillary lymph node dissection was performed in every patient for validation.[3] The breast tissue specimen and nodes taken were sent for fixed H & E examination. The following variables were recorded: mastectomy or breast conserving surgery, SLN identification time, number of SLN's harvested, frozen section result, final H & E result of SLNs, H & E result of axillary lymph nodes, and complications related to the procedure and specifically to the methylene blue dye.

Results

The study patients' ages ranged from 25 to 68 years old (mean 49.45 ± 10.5 years old), all females. Table 1 shows the frequency distribution of clinical variables of study patients. The site of the tumor in the breast is in the upper inner quadrant in half (50%) of the study population. All patients underwent MRM. Majority of the patients (60%) had tumor size of <5cm. Histopathologic types of breast cancer was invasive ductal in 95 percent of the patients.

Table 1. Frequency distribution of clinical variables of study patients.

Variables	Result (N=20)
Tumor Location	
Left	13 (65%)
Right	7 (35%)
Site of Tumor	
Lower outer	1 (5%)
Lower inner	0
Upper outer	9 (45%)
Upper inner	10 (50%)
Breast Tumor Size	
T1	3 (15%)
T2	12 (60%)
T3	5 (25%)
Histopathologic Types of Breast Cancer	
Invasive Ductal	19 (95%)
Ductal Carcinoma In-Situ	1 (5%)

An average of 3 SLNs were removed per patient. In Table 2, results of SLNB were compared to the final histopath of all lymph nodes harvested using H & E, which is our gold standard. Of the 20 patients who underwent SLNB, 5 turned out to be positive for metastasis in frozen section and were truly positive. There were no false positive SLNs. On the other hand, there were 14 out of 15 negative SLNs on frozen section which were truly negative. Only 1 out of 15 was negative on frozen section but was positive on final H & E, which makes the axilla considered positive for metastasis. The accuracy of SLNB is 95.0%, with sensitivity, specificity, positive predictive value, and negative predictive value of 83.3%, 100%, 100%, and 93.3%, respectively.

Table 2. SLNB results and final H & E results of all harvested nodes shown per patient.

		Final biopsy of all harvested axillary nodes using H & E		
		positive	negative	
SLNB	positive	5	0	5
	negative	1	14	15
		6	14	20

Accuracy: 95.0%
Sensitivity: 83.3%
Specificity: 100%
Positive Predictive Value: 100%
Negative Predictive Value: 93.3%

Sentinel lymph node identification ranged from 7 to 39 minutes, averaging 14 minutes.

Discussion

The status of the axilla is one of the most important prognostic factors in breast cancer. In an effort to spare patients from potential complications in axillary lymph node dissection, attempts were made to develop a less invasive technique for identification of positive nodes in the axilla. Giuliano and colleagues successfully adopted SLNB for breast cancer and begun a pilot study in 1991. This study was supported in 1994 after 174 lymphatic mapping procedures were performed using a vital dye injected at the primary breast cancer site. Sentinel nodes were identified in 114 (65.5%) of 174 procedures and accurately predicted axillary nodal status in 109 (95.6%) of 114 cases.[5]

In our study, we were able to identify sentinel lymph nodes in all of our procedures with accuracy rate of 95.0%, comparable with the accuracy rates of studies done by Giuliano, et al.[5] and Merdad, et al.[2] at 95.6% and 96.8%, respectively, and even higher than in the study of Moghimi, et al.[8] and Varghese, et al.[9] at 90.9% and 85.7%, respectively. In a study also done by Varghese, et al.[10] comparing the accuracy of methylene blue alone versus combined methylene blue and radioactive colloid in sentinel lymph node localization, the accuracy using methylene blue alone is 87.4% versus 83.8% using combined methylene blue and radioactive colloid. (Table 3)

Table 3. Comparison of accuracy and false negative rate of sentinel lymph node biopsy using methylene blue dye in different studies.

Study	Year	Dye Used	Accuracy	Negative FalseRate
Giuliano[5]	1994	isosulfan blue lymphazurin	95.6%	4.3%
Merdad[2]	2007	methylene blue (58.9%) lymphazurin (27.8%) lymphazurin + radioisotope (13.3%)	96.8%	3.3%
Varghese[10]	2007	methylene blue	87.4%	3.7%
Moghimi[8]	2009	99m Tc-colloidal albumin + Patent Blue VI	90.9%	8%
This study	2010	methylene blue	95.0%	6.7%

SLNB was carried out safely without major complications and undue reactions. The false negative rate was 6.7% because of a limited sample size. Nevertheless, this is perfectly acceptable compared to those reported in the previous studies which ranged from 0-29% with an overall 7.3% average.[2] In a study by Fearmonti, et al.[6] in multicentric and multifocal breast cancers, the overall false negative rate of SLNB was

15% but Nolasco, et al.[7] had 0% false negative rate using methylene blue dye. Merdad, et al.[2] reported a false negative rate of 3.3%.

Issues remain regarding various technical identification aspects of SLNB. Some authors advocate a single technique using either blue dye or isotope alone, while others maintain that a combination approach to identify SLN is preferable. In this study, we used methylene blue alone. Giuliano, et al.[5] used the blue dye alone for detecting SLNs and reported identification rate to be 93.5% to 98% while Varghese, et al.[9] reported an identification rate of 97.6%. This study's identification rate was 100%. Methods described in this study have proven valid in detecting SLN. These results are fully acceptable when compared with previous studies.

The growing evidence of safety and accuracy of sentinel lymph node biopsy using methylene blue dye as a viable alternative method gives no reason to deny breast cancer patients the chance to enjoy the benefit of a limited axillary dissection.

Conclusion

The accuracy of sentinel lymph node biopsy using methylene blue dye in predicting nodal metastases is 95.0% in VMMC Breast Center.

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