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ORIGINAL ARTICLE

SUBAREOLAR VERSUS PERITUMORAL INJECTION OF METHYLENE BLUE FOR SENTINEL LYMPH NODE DETECTION IN CASES OF EARLY BREAST CANCER

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Abstract

Aim: To compare between subareolar and peritumoral injection of methylene blue dye for proper detection of sentinel lymph in cancer breast.

Method: Eighty female patients with early breast cancer were randomly divided into two equal groups. In the first group blue dye was injected in the subareolar area. In the second group the dye was injected in the peritumoral region. Intra-operative identification of sentinel lymph node(s) was done and then all patients were subjected to complete axillary lymph nodes dissection. Histopathology examination of the tumor and all axillary lymph nodes including the sentinel node(s) was performed using haematoxylin and eosin stain.

Results: Identification rate of the sentinel node was 100% in group A and 86.7% in group B. False negative rate was 0% & sensitivity was 100% in both groups. Specificity was 80% in group A and 87.5% in group B. Positive predictive value was 71.43% and 83.3% in both group A & B. Negative predictive value was 100% for both groups.

Conclusion: We recommend usage of methylene blue subareolar injection as a safe and accurate technique for identification of sentinel lymph node in early cancer breast patients.

Keywords: SLN identification, axillary dissection.

INTRODUCTION

The clinical course of breast cancer varies from patient to patient. Prognostic factors can be used to predict the natural history of a tumor, usually in terms of disease-free survival. Although multiple prognostic factors have been described, those in standard use today include axillary lymph node status, tumor size, histological subtype, nuclear or histological grade, and ER and PR status. The presence of metastases to the axillary nodes is the single most important prognostic factor in breast cancer.[1,2]

Axillary dissection has long been associated with multiple complications and hence other techniques for axillary staging as axillary node sampling and sentinel lymph node biopsy are being switched to.[3]

Standard axillary lymph node dissection involves the removal of the level I and II axillary lymph nodes. The level III axillary nodes were once routinely included in the dissection but are no longer included because removal of these nodes increases the risk of lymphedema without providing significant additional prognostic information.[4]

Four-node axillary sampling was pioneered in the Edinburgh breast unit.[5-7] In this technique sampling of the firmest or largest four nodes in levels, I, II and or III is done.[8] Patients with negative axillary node sample had a significantly lower arm morbidity than those that underwent axillary clearance. On the other hand, random axillary sampling procedures as well as axillary lymph nodes dissection (ALND) limited to level I can miss metastases in 20% to 25% of cases.[9]

With the institution of screening mammography guidelines in many countries between 1980 and 1987, there was a doubling in the incidence of small breast cancers (≤ 2 cm) with a concomitant decrease by 27% in the incidence of larger breast cancers (≥ 3 cm)(10). As the size of primary tumor has decreased, the frequency of axillary nodal involvement has decreased (less than half of women with invasive breast cancer are node positive) raising more the concept of sentinel node biopsy (SNB).[11]

Physical examination of axillary nodal involvement is unreliable method for the assessment of axillary lymph node status as it is associated with a false negative rate of 29%to 38 %.[12,13] Assessment of axilla with various radiographic method as mammography, computed tomography, positron emission tomography was also associated with equally unaccepted false negative rate.[14,15] All these were factors for the great concern of introduction of the concept of sentinel lymph node in cases of early breast cancer.

A sentinel lymph node is defined as the first lymph node in a regional basin that receives lymphatic drainage from the site of a primary tumor. For more than a decade, SLN biopsy in breast cancer patients is used to predict axillary lymph node status and avoid ALND if possible. Sentinel nodes are identified with either blue-dye, radioactive tracer or their combination.[16]

The aim of this study was to compare between subareolar and peritumoral injection of methylene blue dye as a method for proper detection of sentinel lymph node in cases of operable female breast cancer with no clinically nodal metastasis.

PATIENTS AND METHODS

The study had been approved by Alexandria Faculty of Medicine ethics committee. The study was carried out on eighty females suffering from early breast cancer admitted to surgical oncology department at the Main University Hospital, University of Alexandria from September 2007 to May 2009.

Exclusion criteria included: suspicious palpable malignant axillary lymph nodes, suggested axillary lymph node metastasis by mammogram, prior axillary surgery, multicentric tumours, neoadjuvant chemotherapy or refusal of the procedure by the patient.

All studied patients signed an informed written consent before being submitted to: complete clinical assessment including history, clinical examination, basic laboratory work up, mammography & ultrasound of both breasts. Preoperative malignancy confirmation was done either by fine needle aspiration cytology or Tru cut needle biopsy. Also metastatic work up was done in the form of chest X-ray, abdominal and pelvic ultrasonography and Bone scan when indicated.

Patients were randomly divided by closed envelop method into two groups: group (A) and group (B) using the closed envelope technique. Each group included 40 patients. After induction of anesthesia, patients in group (A) were injected with 2ml methylene blue dye 1% in the subareolar area, while patients in group (B) were injected with 2ml of the blue dye in the peritumoral area (breast parenchyma surrounding the tumour at 3,6,9,12 O'clock). The breast was then massaged for 10-15 minutes to facilitate identification of blue lymphatic vessels and nodes more easily.

Patients then were subjected to either modified radical mastectomy or breast conserving surgery according to the standard protocol including complete axillary lymph node dissection after identification of SLN. Sentinel lymph node(s) was identified by either stained blue or having a blue lymph vessel entering it. (Fig. 1)

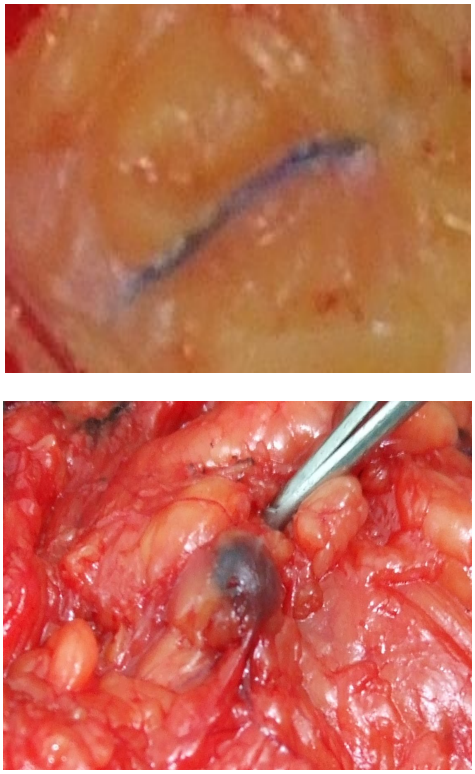

Fig 1. Sentinel lymph vessel (Lt arrow), Sentinel lymph node (Rt arrow).

The statistical analysis of the data obtained in the present study was carried out using SPSS version 15. Qualitative data of the groups was analyzed using Chi-square test, Fisher Exact test and Monte Carlo test.

RESULTS

Both groups were matching in: age, age of menarche, age of menopause, history of pregnancy and lactation and history of oral contraceptive pills (OCP) intake.

The mean clinical size of the tumor in group A was 2.25±1.07cm, range was 0.9-4.1cm. (According to TNM classification, 21 patients (53%) were classified as T1, while 19 (47%) patients were classified as T2.). The mean clinical size of the tumor in group B was 2.55 ± 1.10cm, and the range was 1-4.3 cm. (According to TNM classification, 16 patients (40%) were classified as T1, while 24 (60%) patients were classified as T2). There was no significant statistical difference between the two groups as regard the clinical tumor size (t(p)= 0.757 (0.456)).

In group A there was no lymphatic or vascular invasion noted in 19 (47%) patients while vascular invasion only was noted in 5 (13%) patients and both vascular and lymphatic were noted in 16 (40%) patients. On the other hand 16 (40%) patients in group B did not show vascular nor lymphatic invasion, vascular invasion only was noted in 5 (13%) patients, lymphatic invasion only was noted in 8 (20%) patients and both vascular and lymphatic invasion were noted in 10(25%) patients. This was of no statistical significance (MCp= 0.410)

The mean number of axillary lymph nodes dissected in group A was 13.20 ± 1.74 and the range was 11.00-16.00. While in group B the mean number of dissected nodes was 12.73 ± 1.75 and the range was 10.00-15.00. This was statistically comparable with no significant difference (t(p)= 0.732 (0.470)).

After histological examination of total axillary clearance; 27 patients in group A showed no metastasis to axillary lymph nodes and 13 patients showed malignant deposits in the axillary lymph nodes dissected. In group B, 29 patients showed no metastasis to axillary lymph nodes and 11 patients showed malignant deposits in the axillary lymph nodes dissected.

Methylene blue was very safe in both groups and there were no reported cases of anaphylaxis or hypersensitivity reactions in either group. The sentinel lymph node was stained blue in 32 cases in group A and in 27 cases in group B. The sentinel lymph vessel was successfully identified without staining of any of the nodes in 3 cases in group A. In 5 cases in group A and 8 cases in group B both the sentinel node and the sentinel lymph vessel were stained blue.

In group A we could identify sentinel nodes in all patients (identification rate was 100%). In group B we succeeded to identify the sentinel node in 35 patients (identification rate was 87.5%). This was not of statistically significant difference. (FEp=0.483).

The mean number of sentinel nodes identified in group A was 1.47 ± 0.74 and in group B it was 1.62 ± 0.65. This showed no significant statistical difference (t (p)=0.559 (0.581) (Fig. 2) In the dissected sentinel nodes 18/40 (45%) cases in group A were positive for malignant cells while 14/35 (40%) cases in group B were positive for malignant cells.

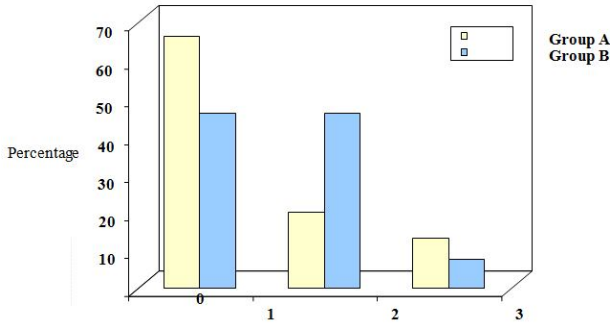

Fig 2. Comparison between the two studied groups according to number of sentinel nodes dissected.

In group A there were 22/40 (55%) cases with negative sentinel nodes for malignant cells; and pathological examination the remaining axillary lymph nodes were all negative for malignant cells as well. The formal pathological examination of the axillary lymph node specimens of those 18 positive cases revealed 13(72%) cases with positive malignant cells and 5(28%) cases with negative axillae for malignant cells in the rest axillary lymph nodes.(i.e. the sentinel node was the only site for metastasis in 5 cases).

In group B there were 21/35 (60%) cases with negative sentinel nodes for malignant cells; they were all negative for malignant cells as well on pathological examination of axillary lymph nodes. While other 14/35 (40%) cases which were positive for malignant cells in their sentinel node biopsies; The pathological examination of axillary lymph node specimens revealed 11(79%) cases with positive malignant cells and 3(21%) cases with negative axilla for malignant cells.(i.e. the sentinel node was the only site for metastasis in 3 cases). Table 1.

These results mean that the sensitivity of both injection techniques is 100%. In group A Specificity was 80%.In group B specificity was 87.5%. Positive predictive value was 71.43% in group A. In group B the positive predictive value was 83.3%. In both groups the negative predictive value was 100%.

Table 1. Agreement between the pathological examination of sentinel nodes harvested and complete formal pathological examination of the axillary lymph node dissected.

			Pathological findings					
			-ve		+ve		Total	
SSLN	Group A	-ve	22	100.0	0	0.0	22	100.0
		+ve	5	27.7	13	72.3	18	100.0
		Total	27	67.5	13	32.5	40	100.0
	Sensitivity		100.0		Specificity		80.0	
	PPV		71.43		NPV		100.0	
	Group B	-ve	21	100.0	0	0.0	21	100.0
		+ve	3	21.4	11	78.6	14	100.0
		Total	24	68.5	11	31.5	35	100.0
	Sensitivity		100.0		Specificity		87.5	
	PPV		83.3		NPV		100.0	

PPV: Positive predictive value. **NPV:** Negative predictive value.

DISCUSSION

Because it is cheap and safe many institutions use blue dye as contrast of first choice. Furthermore, there is no need for nuclear medicine department and gamma probes, so SLN procedure can be performed even in small hospitals or hospitals with limited financial support.[17,18]

Peritumoral injection of blue dye and/or radioactive tracer has achieved wide variable identification rates from 21 to100%. The problems of using the peritumoral injection method arise when the tumor is multifocal, non-palpable and located in the upper outer quadrant of the breast because of the shine-through effect when using the radioactive tracer as well as the blue field of operation with the blue dye.[19]

The growing consensus that the mammary gland and its overlying skin share a common developmental origin and therefore lymphatic drainage suggests that it is feasible to simplify and standardize the SNB technique by injecting the blue dye in the subareolar region.[20]

False negative rate is the most important factor that reflects the mapping accuracy as patients with negative sentinel nodes are not supposed to have further axillary lymph node dissection. If a sentinel node which tests negative for tumor cells at histological examination is removed while a tumor-positive lymph node remains in the axilla, the disease will be under staged, leaving the patient at risk both for local and regional recurrence of disease and for metastasis. A false-negative rate of 5% or less is mentioned frequently in surgical literature as a goal for surgeons performing SLNB.[21,22]

In the current study the false negative rate was 0% for both groups. This could be explained by the relatively younger mean age for both groups. In fact observations of the breast physiology revealed that the number of the breast lymphatics available to absorb and transport dye is often reduced with age as the breast parenchyma is replaced with age by fat resulting in reduced lymphatic number and probably increasing false negative results.

The increase in the size of the tumor together with the increased number of axillary lymph nodes involved cause blockage of the lymphatics, thus increasing the false negative rate. This was stressed up on by Chu et al.[23] who evaluated clinico-pathologic features of 157 patients who underwent SLN biopsy followed by ALND to determine risk factors for non-sentinel node involvement. They found that primary tumor size and extent of SLN pathology -mainly the perinodal infiltration- were strong predictors of non-SLN disease.

In the present study we stressed upon the negative state of axillary lymph nodes by clinical examination as well as by imaging procedures (mammography and sonography). The use of imaging procedures to include or exclude patients candidate for sentinel node procedure was not conducted in most sentinel node studies although Lanng et al.[24] concluded in their study that clinical assessment of axillary LNs as a criterion for offering the SN procedure is of little value.

In review of literature, studies comparing subareolar versus peritumoral injection of blue dye are very few to our knowledge including the study of Kavallaris et al[15] who achieved identification rate 91.7% for the SA group and 80.9% for the PT group. The false negative rate was

3.6% in the SA group and 11.8% in the PT group and hence they concluded from their study that the higher identification rate of SA versus PT localization as well as its acceptable low false negative rate allows the SA localization technique to replace ALND of early breast cancer patients in environments without access to nuclear medicine. On the contrary, Baichev et al[25] whose results were in favor of the PT injection technique as the false negative rate was 31.2% in the SA group while it was 9.4% for the PT group. In review of the Egyptian literature, only Rageh[26] compared the SA and PT injection of blue dye (methylene blue). The identification rate was 85% and 55% in the SA and PT groups respectively. In conclusion: The subareolar injection of the blue dye is as accurate as peritumoral injection. Its diagnostic yield is even higher because it is associated with a higher percentage of identification of SLN. In experienced hands, methylene blue alone is a highly sensitive method of detecting SLNs. It is a cheaper alternative and has the advantage of avoiding the occurrence of allergic complications noticed with the other vital dyes.

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