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Added value of blue dye injection in sentinel node biopsy of breast cancer patients: Do all patients need blue dye?

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ABSTRACT

Background: In the current study, we evaluated the incremental value of blue dye injection in sentinel node mapping of early breast cancer patients. We specially considered the experience of the surgeons and lymphoscintigraphy results in this regard.
Methods: 605 patients with early stage breast cancer were retrospectively evaluated in the study. Patients underwent sentinel node mapping using combined radiotracer and blue dye techniques. Lymphoscintiraphy was also performed for 590 patients. Blue dye, radioisotope, and overall success rates in identifying the sentinel lymph node were evaluated in different patient groups. The benefit of blue dye and radioisotope in identifying the sentinel lymph nodes was also evaluated.
Results: Marginal benefits of both blue dye and isotope for overall sentinel node detection as well as pathologically involved sentinel nodes were statistically higher in inexperienced surgeons and in patients with sentinel node visualization failure. In the patients with sentinel node visualization on lymphoscintigraphy, 6 sentinel nodes were detected by blue dye only. All these six nodes were harvested by inexperienced surgeons. On the other hand 8 sentinel nodes were detected by dye only in the patients with sentinel node non-visualization. All these nodes were harvested by experienced surgeons.
Conclusions: The use of blue dye should be reserved for inexperienced surgeons during their learning phase and for those patients in whom lymphoscintigraphy failed to show any uptake in the axilla.

1. Introduction

Sentinel node biopsy is the standard of care for axillary staging in patients with early stage breast cancer. It avoids the morbidity associated with axillary lymph node dissection in patients with pathologically negative sentinel nodes [1,2].

Two commonly performed methods for sentinel node mapping during surgery include use of the radiotracer alone or in combination with blue dye. Although each of these methods has been used with acceptable results [3,4] several groups have recommended that the combined approach can increase detection rate and decrease false negative rate [5,6]. However the added value of blue dyes over radiotracer alone technique is considered minimal or "marginal" by few authors [7,8]. Although adverse reaction to blue dyes are considerably less significant than previously thought [9,10] blue dye injection carries a risk of adverse reactions including blue discoloration and tattooing of skin, and allergic reactions [11,12].

In the current study, we evaluated the incremental value of blue dye injection in sentinel node mapping of early breast cancer patients. We specially considered the experience of the surgeons and lymphoscintigraphy results in this regard.

2. Material and methods

605 patients (from March 2005 to March 2013) with early stage breast cancer (diagnosed either by excisional biopsy or core needle biopsy) were retrospectively evaluated. Patients underwent sentinel node mapping using combined radiotracer and blue dye techniques. Patients received intradermal injection of the ^{99m}Tc-Antimony sulfide colloid (in 391 patients) or ^{99m}Tc-Phytate (in 214 patients) [13] (0.5 mCi for 1-day and 1 mCi for 2-day protocols).

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Table 1
Characteristics of the patients.

Number of patients	605
Age of the patients	47 ± 18
Histology	
Ductal	405
Lobular	185
Other	25
Type of biopsy	
Core needle	482
Excisional	123
Tumor size	2.3 ± 1.6
Patients with axillary involvement	119
Median number of harvested sentinel node in the patients (range)	1(1–4)

After injection of the radiotracer, gentle massage was applied for 1 min. Lymphoscintiraphy was also performed as described elsewhere for 590 patients (using a dual head E.CAM Siemens or single head SOPHA gamma camera) [14,15].

The sentinel nodes were harvested during surgery using a hand-held gamma probe (RMD navigator or Europrobe) as well as blue dye technique. For the blue dye technique, patients were injected with Patent blue V (395 patients) or Methylene blue (210 patients) after induction of anesthesia in a sub-dermal fashion. Harvested sentinel nodes were sent to the pathologist for frozen section and/or touch imprint cytology. Axillary lymph node dissection was performed in patients with positive sentinel nodes.

Blue dye, radioisotope, and overall success rates in identifying the sentinel lymph node were evaluated in different patient groups. The benefit of blue dye and radioisotope in identifying the sentinel lymph nodes (overall as well as positive sentinel nodes) was also evaluated.

The study was approved by the local ethical committee of the Mashhad University of Medical Sciences.

2.1. Statistical analysis

Continuous variables were expressed as mean ± SD. Chi-square test (or exact test) was used for comparison between groups. All statistical analyses were performed by SPSS version 11.5 and *p*-values less than 0.05 were considered statistically significant.

3. Results

Table 1 shows the characteristics of included patients. Table 2 shows Dye, isotope, and overall success rates in identifying the sentinel nodes. Overall detection rate was 86.4%, 91%, and 93.7% for blue dye, radiotracer, and combined method respectively. Detection rates for methylene blue and patent blue V were 86.2%, and 86.6% respectively (statistically non-significant difference) and for ^{99m}Tc-antimony sulfide colloid, and ^{99m}Tc-phytate were 91.3%, and 90.6% respectively (statistically non-significant difference). Detection rate was statistically different between experienced and inexperienced surgeons (experienced surgeons had passed the learning curve period which encompassed axillary dissection in addition to sentinel node biopsy in 30 patients). Experienced surgeons had higher detection rate. Four experienced and three inexperienced surgeons were involved in the study period. Detection rate was also statistically higher in patients with visualized sentinel node on lymphoscintigraphy images.

Table 3 shows the marginal benefit of dye and isotope for identifying sentinel nodes. Marginal benefits of both blue dye and isotope were statistically higher in inexperienced surgeons and in patients with sentinel node visualization failure on lymphoscintigraphy images. In the patients with sentinel node visualization on lymphoscintigraphy, 6 sentinel nodes were detected by blue dye only (1% of the harvested nodes). All these six nodes were harvested by inexperienced surgeons. On the other hand 8 sentinel nodes (16.3% of the harvested nodes) were detected by dye only in the patients with sentinel node non-visualization. All these nodes were harvested by experienced surgeons.

Marginal benefits of blue dye and isotope were also statistically higher for identifying involved sentinel nodes by inexperienced surgeons and in patients with sentinel node visualization failure on lymphoscintigraphy images (Table 4). In one patient with visualized sentinel node on lymphoscintigraphy, the involved sentinel node was identified by blue dye alone. This patient was also operated on by an inexperienced surgeon.

Addition of blue dye, and radioisotope decreased the false negative rate 4/114 (3.5%) and 7/114 (6.1%) respectively as shown in Table 4.

4. Discussion

The rationale behind using two agents (radiotracer and blue dye) for sentinel node mapping is to increase detection rate of sentinel nodes and more importantly to decrease the false negative rate of the procedure [5,16–19]. This approach is also valid for sentinel node biopsy of other tumors besides breast cancer [20–22]. Our study confirmed this point as overall detection rate was higher using the combined blue dye/radiotracer method. Blue dye also contributed to detection of sentinel nodes which were

Table 2
Dye, isotope, and overall success rates in identifying the sentinel nodes (the numbers are patients).

	Dye success		Isotope success		Combined success	
	N/total	%	*N*/total	%	*N*/total	%
Experienced surgeons ($n = 545$)	MB 165/191	MB 89.1%	P 179/185	P 93.7%	–	–
	PB 320/354	PB 88.9%	AC 333/360	AC 94%		
	Total 485/545	Total 89%	Total 512/545	Total 94	519/545	95.2
Inexperienced surgeons ($n = 60$)	MB 16/23	MB 64%	P 15/25	P 65.2%	–	–
	PB 22/37	PB 62.8%	AC 24/35	AC 64.9%		
	Total 38/60	Total 63.3%	Total 39/60	Total 65%	48/60	80%
p-Value	<0.0001		<0.0001		<0.0001	
Sentinel node visualized on lymphoscintigraphy imaging ($n = 550$)	MB 174/190	MB 92.5%	P 184/188	P 96.8%	–	–
	PB 334/360	PB 92.5%	AC 348/362	AC 96.6%		
	Total 508/550	Total 92.4%	Total 532/550	Total 96.7%	538/550	97.8%
Sentinel node not visualized on lymphoscintigraphy imaging ($n = 40$)	MB 5/14	MB 38.5%	P 5/13	P 35.7%	–	–
	PB 10/26	PB 37%	AC 8/27	AC 30.8%		
	Total 15/40	Total 37.5%	Total 13/40	Total 32.5%	22/40	55%
p-Value	<0.0001		<0.0001		<0.0001	

MB: Methylene blue, PB: Patent blue V, P: ^{99m}Tc-phytate, AC: ^{99m}Tc-antimony sulfide colloid.