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Sentinel lymph node biopsy in node negative early breast cancer patients with Methylene blue dye only method- A Preliminary Experience

Oncology

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ABSTRACT

Introduction:
The combination of both isosulphan blue and the radioactive sulphur colloid gives the best result and is the standard procedure for performing Sentinel lymph node biopsy (SLNB) in node negative early breast cancer patients to stage the axilla. Isosulphan blue is expensive and nuclear medicine facility is not widely available. An affordable, equally efficient alternative could be the use of methylene blue dye alone for doing SLNB.

Materials and methods:
Of the 81 node negative early breast cancer patients included in the study, 46 were subjected to the combination method of methylene blue and radioactive sulphur colloid with validation done in the first 20 patients and 35 to methylene blue only for carrying out SLNB. All the patients in the dye only method were subjected to axillary lymph node dissection (ALND) following SLNB.

Results:
Sentinel lymph nodes identification rate in the combination method was 97.8% and methylene blue dye was 91.4%. False negative rate in combination method and blue dye only method were 0 and 9% respectively. All other results were concurrent. Sensitivity and specificity of the combination method was100% and in methylene blue dye only method was 90.91% and 100% respectively. None of the patients had any major complications pertaining to methylene blue dye injection.

Conclusion:
The results of methylene blue dye alone are comparable to the combination method for SLNB. When nuclear medicine facilities are not available, the use of blue dye alone could be justified to carry out SLNB to avoid ALND when not necessary. However, this needs validation by further studies in large numbers.

KEYWORDS:

Sentinel lymph node, methylene blue dye, early breast cancer

Introduction:
Sentinel lymph node biopsy (SLNB) is the accepted standard procedure for node negative early breast cancer patients to stage the axilla. The combination method of using isosulphan blue and radioactive sulphur colloid for performing the SLNB gives the best result and is the recommended method. However, Isosulphan blue is costly and not readily available and not all the centers are equipped with nuclear medicine facility. An affordable and equally efficient alternative could be the use of methylene blue dye alone for performing SLNB.

Objective:
To compare the use of methylene blue dye as a single agent and in combination with radioactive Sulphur colloid for performing sentinel lymph node biopsy in women with early breast cancer

Materials and methods:
This is a prospective study done in our institute from August 2014 to April 2017. Informed written consents were taken from all the patients who were included in this study. 81 consecutive patients with pathologically proven,clinically node negative early breast cancer i.e. T1/2, N0, M0 were included in the study. Patients with T3, 4 lesions, multicentric/multifocal primaries, palpable axillary lymph nodes, systemic metastases, pregnant women and lactating mothers were excluded from the study.

As a standard procedure the combination method of blue dye (methylene blue) and radioactive sulphur colloid was used in 46 node negative early breast cancer patients for doing SLNB and as a part of validation level I, II and III axillary lymph node dissection was done in the first 20 cases. Due to the non-functioning of the gamma probe, we decided to continue performing SLNB with methylene blue dye alone in the next consecutive 35 patients of node negative early breast cancer patients which was followed by level I and II axillary lymphnode clearance in all of them irrespective of the frozen section report as performing SLNB with methylene blue dye alone is not the standard of care and appropriate validation of this method was needed

Technetium-99 m labeled radioactive sulfur colloid of 0.5 millicurie was injected in the combination method in the morning on the day of surgery. The site of injection was subareolar, subdermal. Methylene blue dye 1% (3 to 5 ml) intraparenchymal, peritumoral injection was given in the pre-operative room just before shifting the patient inside the operation theatre. All the hot and blue lymphnodes were removed as sentinel lymph nodes followed by which level I, II and III axillary dissection done in the first 20 patients of the combination method group and all the patients of the methylene blue dye only method. Among the remaining 26 patients of the combination method for whom no validation was intended, the performance of axillary lymph node dissection I-III was based on the frozen section report. While harvesting the SLN, rule of 10% was followed for the hot nodes and blue node or the node to which the blue stained afferent lymphatic reaches was considered as a blue node. The primary breast lesion was addressed with either mastectomy or wide local excision with 1 to 2 cm margin.

Results:
Average age of the patients was 46.6 years ranging from 32 to 65 years. Twenty-six patients were premenopausal and 55 postmenopausal. In 42 patients (52%), the primary was on the left side and 39 patients (48%) on the right. In majority of the patients the tumour was located in the upper outer quadrant (30 patients, 37%). In 24 patients (29.6%) primary was located in lower outer quadrant, 16 patients (19.8%) in upper inner quadrant, and 8 patients (9.9%) in central quadrant and 3 patients (3.7%) in lower inner quadrant. The average size of the tumour was 3.5 cm (range 1.5 to 5cm) with majority of the tumours being T2 (n= 61, 75.3%). The above mentioned basic demographic profile was equally distributed in both the groups. Fifty-two patients (64.2%) opted for breast conservation surgery (BCS) and the remaining underwent mastectomy.

Sentinel lymph nodes were identified in 45/46 patients in the combination method and 32/35 patients in the methylene blue dye only method (identification rate of 97.82% and 91.43% respectively). The

average number of SLN harvested in the combination method was 3.5 and in the methylene blue dye only method is 3. Results of the study are summarized in table 1 and 2. False negative rate of methylene blue dye only method is 9%. None of the patients had any major complications pertaining to methylene blue except for minor complications such as bluish discoloration of urine in 13 patients (16%) and skin tattooing in 4 (4.9%)

Table 1

	Combination method (n=20)	Blue dye only method (n=35)
SLNB negative ALND negative	16	24
SLNB positive ALND negative	4	9
SLNB negative ALND positive	0	1
SLNB positive ALND positive	0	1

Table 2

	Combination method (n=46) %	Blue dye only method (n=35) %
Identification rate	97.82	91.43
Concordance rate	100	100
False negative rate	0	9
Positive predictive value	100	100
Negative predictive value	100	96
Sensitivity	100	90.91

Discussion:

The advantages of using methylene blue for performing sentinel lymph node dissection are multiple and as follows. It is cheaper (2) readily available, less serious systemic complications (3-6) and a good learning curve (7) Only a few case reports have been published in literature regarding skin and fat necrosis (5,8,9,10) associated with methylene blue dye injection.

Various studies have shown sentinel lymph node identification rate ranging from 91% to 100% with methylene blue dye in combination with the radioactive sulphur colloid (2,4,11–17). The comparison of those results with our study has been summarized in table 3. The SLN identification rate were comparable in both the groups of the present study and to the available literature. This implies that methylene blue is a safe and effective alternative to isosulphan blue in performing sentinel lymph node biopsy.

Table 3

Study	SLNB method	No. of patients in the study	No. of patients subjected to MBD	SLN identification rate
Blessing WD et al, 2002	Combination MBD Vs IBD	199	112	92
Simmons R et al, 2003	Combination MBD	112	112	92.8
Nour A., 2004	Combination MBD	56	56	91.1
Varghese P et al, 2008 (RCT)	MBD only vs combination	329	173	96.5
S.P. Somashekar et al, 2008	Combination MBD	100	100	100
Shirah GR et al, 2011	Combination MBD Vs IBD	194	96	99.1
Our study	MBD alone vs combination	81	81	94.6

Radovanovic et al have done a head on comparison of the blue dye only method using patent blue dye in 50 patients with 100 patients subjected to the combination method of using both the blue dye and the radio isotope(18). They found that false negative rate of blue dye alone method was significantly higher than the combination method (17.6% vs 4.5%). Syme DB et al(19) did a retrospective study of 384 patients who underwent sentinel lymph node biopsy evaluating the efficacy of dye alone method (patent blue) over the combination method. The identification rate was similar in both the groups (96% vs 89%). However, the false negative rate was higher in the dye alone method compared to the combination method (21% vs 2.8%). Meta analysis which included 183 articles and 9306 patients published by Pesek et al(20) demonstrates that the false negative rate of the combination method of using dye and radioactive tracer is significantly less i.e. 5.9% when compared to dye only method in which it was 8.6%. As it was statistically significant it was concluded saying that the combination method is superior. The false negative rate observed in our study (9%) correlates with the above meta-analysis observation.
However, there are studies as the following that showed dye alone method using various dyes as mentioned yielded a good sentinel lymph node identification rate ranging from 77% to 100% with some studies even showing a reasonably acceptable false negative rate. Hung WK et al(21) demonstrated in their randomized control trial comparing blue dye (vital blue) with combined dye and isotope the efficacy of the blue dye alone method with SLN identification rate of 86% and false negative rate of 5%. Motomura et al(22) have shown SLN identification rate of 73.8% with Indocyanine green alone and a false negative rate of 11.1%. Takamaru et al(23) had demonstrated excellent results using the dye alone method utilizing indigocarmine dye for the sentinel lymph node biopsy procedure (SLN identification rate of 96.8% and a false negative rate of 3.6%).

AS Fattahi et al study(24) also showed a sentinel lymph node identification rate of 77% with methylene blue dye alone. However, those who had a negative sentinel node were not subjected to axillary lymph node dissection in this group to detect the false negative rate. Varghese et al(15) did a randomized control study comparing methylene blue dye injection only for SLNB with the combination of radioactive sulphur colloid. In their study as well, they have not done validation for the methylene blue dye only method by completing the axillary dissection in negative SLN patients. Though these two studies have given the SLN identification rates that are acceptable, there isn't any clear and adequate data available on the false negative rate of dye alone method in the current literature. Hence, well conducted large randomized control trials with appropriate validation is required to substantiate its utility as a single agent for use in SLNB.

Conclusion:

Considering the advantages of the methylene blue dye and the widespread non-availability of radioactive sulphur colloid in developing countries methylene blue dye alone can be used to perform SLNB with a reasonable benefit though is not the standard of care. This would avoid the morbidity of Axillary lymph node dissection in significant number of patients with node negative early breast cancer in the above setting.

References:

1. Martin RC, Edwards MJ, Wong SL, Tuttle TM, Carlson DJ, Brown CM, et al. Practical guidelines for optimal gamma probe detection of sentinel lymph nodes in breast cancer: results of a multi-institutional study. For the University of Louisville Breast Cancer Study Group. Surgery. 2000 Aug;128(2):139–44.
2. Gold HT, Do HT, Osborne MP. Cost-effectiveness of isosulfan blue vs. methylene blue dye in sentinel node biopsy. ASCO Meet Abstr. 2005 Jun 1;23(16_suppl):6103.
3. Newman LA. Lymphatic mapping and sentinel lymph node biopsy in breast cancer patients: a comprehensive review of variations in performance and technique. J Am Coll Surg. 2004 Nov;199(5):804–16.
4. Simmons R, Thevarajah S, Brennan MB, Christos P, Osborne M. Methylene blue dye as an alternative to isosulfan blue dye for sentinel lymph node localization. Ann Surg Oncol. 2003 Apr;10(3):242–7.
5. Salhab M, Al sarakbi W, Mokbel K. Skin and fat necrosis of the breast following methylene blue dye injection for sentinel node biopsy in a patient with breast cancer. Int Semin Surg Oncol ISSO. 2005 Nov 28;2:26.
6. Aydogan F, Celik V, Uras C, Salihoglu Z, Topuz U. 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. 2008 Feb;195(2):277–8.
7. East JM, Valentine CS, Kanchev E, Blake GO. Sentinel lymph node biopsy for breast cancer using methylene blue dye manifests a short learning curve among experienced surgeons: a prospective tabular cumulative sum (CUSUM) analysis. BMC Surg. 2009 Jan 27;9(1):2.
8. Kang SS, Han B-K, Ko EY, Shin J-H, Cho EY, Lee JE, et al. Methylene Blue Dye–Related Changes in the Breast After Sentinel Lymph Node Localization. J Ultrasound Med. 2011 Dec 1;30(12):1711–21.
9. Ha KY, Parish D, Hamilton R, Wang JC. Fat necrosis in the breast from methylene blue dye injection. Proc Bayl Univ Med Cent. 2013 Jul;26(3):298–9.
10. Reyes F. Complications of Methylene Blue Dye in Breast Surgery: Case Reports and

Review of the Literature. J Cancer. 2011;20.
11. Blessing WD, Stolier AJ, Teng SC, Bolton JS, Fuhrman GM. A comparison of methylene blue and lymphazurin in breast cancer sentinel node mapping. Am J Surg. 2002 Oct;184(4):341–5.
12. Eldrageely K, Vargas MP, Khalkhali I, Venegas R, Burla M, Gonzalez KD, et al. Sentinel lymph node mapping of breast cancer: a case-control study of methylene blue tracer compared to isosulfan blue. Am Surg. 2004 Oct;70(10):872–5.
13. Golshan M, Nakhlis F. Can methylene blue only be used in sentinel lymph node biopsy for breast cancer? Breast J. 2006 Oct;12(5):428–30.
14. Nour A. Efficacy of methylene blue dye in localization of sentinel lymph node in breast cancer patients. Breast J. 2004 Oct;10(5):388–91.
15. 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. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2007 Mar;33(2):147–52.
16. Somashekhar SP, Zaveri Shabber S, Udupa Venkatesh K, Venkatachala K, Parameshwaran, Vasan Thirumalai MM. Sentinel lymphnode biopsy in early breast cancer using methylene blue dye and radioactive sulphur colloid — a single institution Indian experience. Indian J Surg. 2008 Jun;70(3):111–9.
17. Shirah GR, Bouton ME, Komenaka IK. Occurrence of prolonged injection site mass with methylene blue but not isosulfan blue after the sentinel node procedure. Arch Surg Chic Ill 1960. 2011 Feb;146(2):137–41.
18. Radovanovic Z, Golubovic A, Plzak A, Stojiljkovic B, Radovanovic D. Blue dye versus combined blue dye—radioactive tracer technique in detection of sentinel lymph node in breast cancer. Eur J Surg Oncol. 2004 Nov 1;30(9):913–7.
19. Syme DBY, Collins JP, Mann GB. Comparison of blue dye and isotope with blue dye alone in breast sentinel node biopsy. ANZ J Surg. 2005 Sep;75(9):817–21.
20. Pesek S, Ashikaga T, Krag LE, Krag D. The false-negative rate of sentinel node biopsy in patients with breast cancer: a meta-analysis. World J Surg. 2012 Sep;36(9):2239–51.
21. Hung WK, Chan CM, Ying M, Chong SF, Mak KL, Yip AWC. Randomized clinical trial comparing blue dye with combined dye and isotope for sentinel lymph node biopsy in breast cancer. Br J Surg. 2005 Dec;92(12):1494–7.
22. Motomura K, Inaji H, Komoike Y, Kasugai T, Noguchi S, Koyama H. Sentinel node biopsy guided by indocyanine green dye in breast cancer patients. Jpn J Clin Oncol. 1999 Dec;29(12):604–7.
23. Takamaru T, Kutomi G, Satomi F, Shima H, Ohno K, Kameshima H, et al. Use of the dye-guided sentinel lymph node biopsy method alone for breast cancer metastasis to avoid unnecessary axillary lymph node dissection. Exp Ther Med. 2014 Feb;7(2):456–60.
24. Fattahi AS, Tavassoli A, Rohbakhshfar O, Sadeghi R, Abdollahi A, Forghani MN. Can methylene blue dye be used as an alternative to patent blue dye to find the sentinel lymph node in breast cancer surgery? J Res Med Sci Off J Isfahan Univ Med Sci. 2014 Oct;19(10):918–22.