International Surgery Journal
Parasuraman M et al. Int Surg J. 2018 Jan;5(1):1-10
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: http://dx.doi.org/10.18203/2349-2902.isj20175879

Review Article

Use of methylene blue for the detection of sentinel lymph node in breast cancer: a systematic review and meta-analysis

Madhivadhanam Parasuraman, Bhanumati Giridharan*, Vijaylakshmi

Department of General Surgery, ESIC Medical College and PGIMSR, Chennai, Tamil Nadu, India

Received: 27 September 2017
Accepted: 31 October 2017

***Correspondence:**
Dr. Bhanumati Giridharan,
E-mail: dr.bhanumati@gmail.com

ABSTRACT

Sentinel lymph node biopsy is the widely acceptable method for the examination of the breast cancer in the patients. This biopsy is considered as the best method for identifying the axillary involvement. Various dyes are used in this biopsy to find the sentinel lymph node. However, methylene blue dye (MBD) is considered to have a low risk of anaphylaxis, be cost effective and widely available.

A systematic review and meta-analysis is performed on the utilisation of the methylene blue dye in the sentinel lymph node biopsy in the examination of breast cancer.

Eight studies were appropriate for the inclusion criteria that were analysed systematically wherein meta- analysis is performed on studies which had ample data that comparatively analysed the efficiency of methylene blue. However, only two studies were selected for meta- analysis based on the availability of data.

Systematic review reveals that methylene blue dye can be used as the best alternative when compared to other dyes in the detection of sentinel lymph node in the patients with breast cancer. However, the meta-analysis of two studies revealed no statistical significance defining the efficacy of methylene blue for sentinel lymph node detection.

Keywords: Breast cancer, Methylene blue dye, Sentinel lymph node biopsy

INTRODUCTION

In order to examine the breast cancer in the patients for the local metastasis, sentinel node mapping has been thought as the favourable method. This method is on the basis of the path that a cancer cell takes from the primary breast tumour for the metastasis to the local lymph node. The first receiver of the metastatic disease is this lymph node and if this is negative, it can be assumed that all other lymph nodes in that region are not involved by the tumour. This type of mapping was used in the examination and management of the melanoma patients and it caught the widespread attention, as the initial experience was reported by the Morton's group.[1] In spite of the scarcity of the evaluation by the government, methylene blue has been used in the identification of cancer and this dye does not pose severe risks like life-threatening allergic reactions as in the case of lymphazurin.[2,3] Before the sentinel lymph nodes were studied, it was thought that the axillary lymph node dissection had been the proper treatment for the patients with the breast cancer at the early stage.[4,5] In fact, the degree which the axilla is involved is one of the most significant independent prognostic parameters for the tumour incidence and the patient survival.[5,6]

Certain researchers have favoured the application of nuclear medicine techniques to find the sentinel lymph node because of the benefit of simplicity of these methods as compared to the utilisation of dyes.[7,8] If dyes

are used, the surgeon will need a little more of training and the learning curve could be steeper.[9] Post the preliminary training period, the identification rate of sentinel lymph node with the dyes does appear equal to that got with the nuclear medicine techniques, touching 98% in certain latest reports.[10]

Moreover, if the sentinel lymph node is found, the accuracy is found to be the same regardless of the technique employed and the lymph node identification rate. The foremost drawbacks in the radioactive tracer techniques are the technological complexity and expensiveness.[7] Therefore, it is considered that the utilisation of dyes is yet the most viable option cost wise that too in the case of public healthcare services which are with only limited resources that has been a general situation in the developing countries. Various important dyes have been utilised to find the sentinel lymph node such as isosulphan blue, patent blue, and methylene blue.[8,10]

While methylene blue is available easily and considered cheap cost wise, researchers assert that it spreads more quickly in the peripheral tissues, thus staining a major part of the breast with the blue dye preventing the procedure.[11–13] With the use of methylene blue and patent blue, researchers have revealed similar accuracy and sentinel lymph node detection rates.[10,14] When compared to other dyes, there is a lower risk of anaphylaxis with methylene blue.[15] In this regard, the objective of the present study is to do a systematic review and a meta-analysis on the utilisation of the methylene blue for the detection of sentinel lymph node in breast cancer.

METHODS

Search strategy and study selection

The search for the studies was done electronically wherein several medical databases were searched such as EBSCO, MEDLINE (PubMed), and NCBI, EMBASE, ISI and SCOPUS databases for the studies published up to December 2016. Following are the keywords that were used in the search - 'methylene blue in sentinel lymph node biopsy; using methylene blue in SLNB; efficacy of methylene blue in SLNB; methylene blue in SLNB detection.'

PICO methodology

Table 1: PICO methodology.

Population or patient	Patients with breast cancer
Intervention	The use of methylene blue for the detection of sentinel lymph node
Comparison	-
Outcome	Use of methylene blue dye as an effective method for the detection of sentinel lymph node in breast cancer

This study used the PICO (Population, Intervention, Comparison, and Outcome) methodology to elaborate the inclusion parameters for the choice of appropriate studies in the review (Table 1 and 2).

Table 1: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Research studies which included the use of methylene blue for the detection of sentinel lymph node in breast cancer	Research articles that did not include the use of methylene blue dye for the detection of sentinel lymph node in the case of breast cancer
Research articles in English	Research articles in languages other than English
studies within 2006-2016	Studies outside the time frame 2006-2016
Full text research articles	Research articles with incomplete information

Assessment of quality (systematic review) and quantitative analysis (meta- analysis)

The appraisal of research articles critically is called as the assessment of methodological quality and this context is normally used in the systematic review. The employment of Critical Appraisal Skills Programme (CASP) tool helps with the evaluation of the studies chosen on the basis of their quality and this tool can be used to verify if the articles chosen could be included in the systematic review. However, for the meta-analysis, Review Manager (RevMan) software is used.

Description of the studies

The initial search for the studies with regard to the use of methylene blue for SLNB yielded 7881 studies. When the inclusion and exclusion criteria were applied for the studies as mentioned in Table 2, the search narrowed down to only 27 articles which had got the relevance in line with the topic. When further screening was done on the articles on the basis of availability of ample data, only 8 articles were qualified for the systematic review (Table 3). The PRISMA flow diagram (Figure 1) depicts the method of selection of studies for the topic. The characteristics of the research studies considered for the systematic review are as depicted in the Table 4.

DISCUSSION

The present study is the systematic review of the use of the methylene blue for the detection of the sentinel lymph node in breast cancer. All the eight studies considered for this systematic review are fit with regard to the inclusion criteria in the Table 2. All the papers analyse the use of methylene blue in the SLN detection.[16] In a study done by Golshan and Nakhlis it was found that MBD is the only substitute for lymphazurin.

Table 2: Data extraction table.

Author	Study objective	Data collection period	Results	Conclusion
Golshan and Nakhlis[16]	To review the experience of methylene blue to identify the sentinel lymph node	September 2003 - March 2005	The SLN was identified in 136 of 141 patients (96.5%). About 33 of 136 patients (24%) had metastatic disease. No anaphylaxis was noted.	Methylene blue alone is highly sensitive method in the detection of SLN in the case of experts. Avoiding the allergies with MBD is an edge over lymphazurin.
Mathelin et al[19]	To analyse the safety of methylene blue dye (MBD) and compare its efficacy with that of isotopic mapping for sentinel lymph node (SLN) identification in breast cancer	April 2006 - April 2007	The procedure was proved to be safe with 99% success rate. SLN was identified in 65% by MBD, in 73% by lymphoscintigraphy and in 94% by gamma-probe.	MBD is safe and combination mapping in association with digital examination is the best method.
Zaazou et al[20]	To evaluate the effectiveness and accuracy of SLNB using methylene blue dye in predicting axillary nodal status in early breast cancer with clinically impalpable axillary lymph nodes	May 2006 – April 2009	In 94 patients, SLNB was successfully undertaken in 86 patients (91.5%). Accuracy was 95.3%; sensitivity 88.2%; false negative rate 11.8%; negative predicted value 92.8%; rate of metastasis to SLN only without affecting other nodes 26.5%	In the women with the early breast cancer, SLNB done using the methylene blue is the accurate predictor of the status of axillary node.
Sohail et al[26]	To determine the accuracy and feasibility of the procedure to incorporate the sentinel node biopsy in future surgical practice	July 2001 – August 2002	SLN identification rate 93.4% (28 of 30 patients); false negative rate 7.1% (2 of 28 patients); sensitivity 85.7% and specificity 71.4% with positive predictive value 75% and negative predictive value 83.3%	In early breast cancer, the SLN can predict the axillary node status and SLNB can be done with MBD with confidence cost-effectively.
Ozdemir et al[30]	To evaluate the results of sentinel lymph node biopsy (SLNB) with methylene blue in patients with early-stage breast cancer	Not mentioned	SLN identified in 30 of 32 patients (94%); lymph node metastasis not seen in 17 patients in SLN and axilla. Two patients had metastasis in axilla, not in SLN. About 11 had metastasis in SLN and axilla. Accuracy rate 93% and false negativity 15%.	SLNB can be accurately performed with MBD and this dye is alternative for isosulphabe blue.
Fattahi et al[32]	To compare two commonly available blue dyes, methylene blue dye and patent blue dye to detect the sentinel lymph node and to evaluate their local complications	February 2010 - December 2012	Mean tumour size 2.4 cm with standard deviation 0.8 cm. Rate of detection with MBD 77.5% with dye alone and 94.2% with dye and radioisotope. Rate of detection with patent blue 80.1% with dye alone and 92.9% with dye and radioisotope.	MBD has an acceptable detection rate of SLN. With MBD, blue discolouration is also low.
Kasula et al[33]	To assess the accuracy of sentinel lymph node biopsy in detecting axillary metastasis in cases of clinically and sonographically node negative early breast cancer using methylene blue dye	August 2011 - July 2013	SLN was found in 86.7% of the cases. Accuracy of SLN as an indication of axillary status is 92.3%. Sensitivity 87.5%. Negative predictive value 83.3%. Metastasis in SLN without affecting the axillary was 37.5%.	MBD is an acceptable predictor of the status of axillary node in SLNB in the case of early breast cancer.
Paulinelli et al[35]	To compare the patent blue and methylene blue for the detection of the sentinel lymph node in breast cancer patients	Not mentioned	SLN identified in 47 women (68.1%) in patent blue group and 43 women (60.6%) in MBD group. SLNs were affected in 22 cases (51.2%) in patent blue group and 21 cases (48.8%) in MBD. SLN was alone affected in 12 cases (54.5%) in patent blue group and 6 (33.3%) in MBD. No complications or allergies.	MBD as well as patent blue performed in identifying the SLN in the case of breast cancer.

Table 2: Comparison of methylene blue with other dyes.

Author	Methylene Blue Dye	Other dyes	Outcome
Golshan and Nakhlis[16]	Cost effective. No side effects. No allergic or anaphylactic reaction.	Lymphazurin dye (Isosulphan) Cost is higher. Potential side effects. Incidence of between 1% and 3% allergic and anaphylactic reaction.	In the detection of sentinel lymph node, methylene blue is a safer option over lymphazurin. Methylene blue is highly sensitive in detecting the SLNs
Mathelin et al[19]	Molecular weight 319.9 No allergic reaction.	Isosulphan blue dye Molecular weight:543.7 Significant allergic reaction. Patent blue dye Significant allergic reaction.	MBD is safe for the SLN detection. The combined method along with intraoperative digital examination is superior.
Zaazou et al[20]	Accuracy: 95.3% Sensitivity: 88.2% Specificity: 86.7% False negative rate: 11.8% Negative predicted value:92.8 Rate of metastasis 26.5%	-	Sentinel lymph node biopsy done with MBD can predict the axillary node status.
Sohail et al[26]	Accuracy: 93.4% False negative: 7.1% Sensitivity: 85.7% Specificity: 71.4% Negative predicted value: 83.3% Positive predicted value: 75%	-	The status of axillary node can be predicted by sentinel lymph node biopsy.
Ozdemir et al[30]	Cheap Accuracy rate 92.7%. Sensitivity 85% Specificity 100% Negative predicted value 100% Positive predicted value 90% Accuracy 93%	Isosulphan blue dye Costly Hypersensitivity is 0.6 to 2.5% Accuracy rate 88.5%.	Methylene blue can be used to do sentinel lymph node biopsy accurately. This dye can be utilized alternatively for isosulphan blue.
Fattahi et al[32]	Detection rate 77.5% (dye alone). Detection rate with radio tracer 94.2%. Low systemic reaction. Local inflammation 3.2%. Blue tattooing 14.1%.	Patent blue dye Detection rate 80% (dye alone). Detection rate with radio tracer 92.9%. Anaphylaxis. Local inflammation 0.6% Blue tattooing 23.7%.	MBD is a cost-effective and safe dye.
Kasula et al[33]	Identification rate: 86.7% Accuracy: 92.3% Sensitivity: 87.5% Specificity: 45.45% Negative predicted value: 83.3%	-	The axillary node status can be predicted using MBD and it is an acceptable predictor.
Paulinelli et al[35]	Cheaper. No allergic reaction. Interference with oximetry is less. Can be used during pregnancy.	Patent blue Costlier. Allergic reaction is 1% to 2%. Interference with oximetry is more. Cannot be used during pregnancy. Isosulphan blue Costlier. Allergic reaction is 1% to 2%. Interference with oximetry is more. Cannot be used during pregnancy.	MBD can substitute patent blue in sentinel lymph node biopsies at low cost.

This research also finds that methylene blue is safe with rare anaphylaxis. No anaphylactic reaction to methylene blue for sentinel lymph node mapping was reported. The reactions like erythema and necrosis in the breast have been revealed in the superficial injections of the methylene blue.[17] There is occurrence of allergic and anaphylactic reaction between 1% and 3% with lymphazurin.[2,3,18] The reactions may be wheals, blue hives, or cardiovascular collapse. The research performed by Mathelin et al, indicated that intraparenchymal subareolar injection of MBD was safe and no major adverse events or axillary recurrences after a mean follow-up of 28 months.[19]

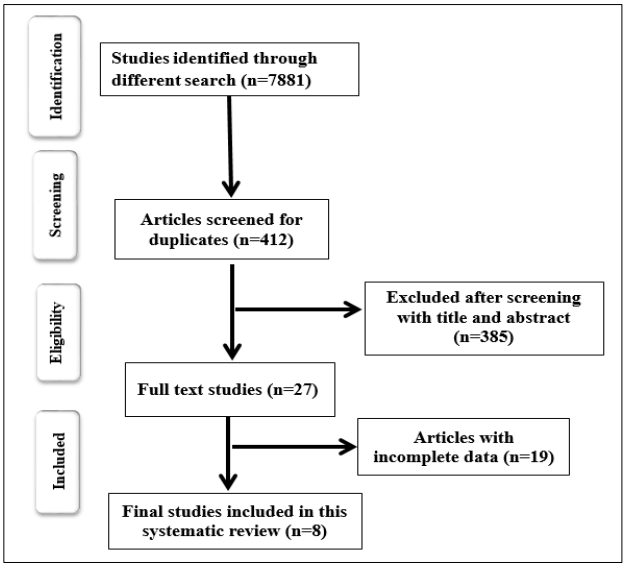

Figure 1: PRISMA flow diagram.

However, in the research done by Mathelin et al, necrosis was not found on contrary to the published material.[19] The study of Stradling et al, revealed 5 necrotic lesions (21%) when 3ml to 5ml of MBD (full strength 1%, 10mg/ml) was injected in 24 patients.[17] Parenchyma and the skin were injected with methylene blue dye. The patients did not need any surgical debridement. The study of Mathelin et al, reveals that the procedure with MBD has 99% success rate.[19] In this study, the identification of SLNs, with MBD, was 65%; with lymphoscintigraphy, 73%; and with gamma-probe, 94%.

In a study done by Zaazou et al, the usage of blue dye was proved to be successful and the success rate was reported to be 91.5% compared to the prior studies in which the identification rate of the sentinel node ranged from 83% to 93% with the use of methylene blued dye.[12,19,21,22] The remainder of the patients, who had not shown the dye in the sentinel lymph nodes revealed involvement of these nodes with malignancy that affected the non-sentinel axillary nodes. The false-negative results show the accuracy of sentinel lymph node biopsy as though the negative sentinel node is removed, and the positive node is left in the axilla. There is a chance that the disease can be under-staged, thereby letting the patient be at risk for recurrence. If found successfully, the SLNB can correctly predict the axillary node status at 95.3% (82 of 86). The false negative results are at 11.8% (4 of 34). This can be compared with other reports revealing 0-17% false negative results.[23,24] These false negative outcomes could be due to the insufficient experience of the surgeons with the sentinel lymph node biopsy procedure in addition due to the result of tumour infiltration of the primary node draining the tumour. Fenaroli et al revealed that axillary dissection can be spared in SLNB in about half of cases of early breast cancer.[25] From this, it can be clarified that the SLNB permits the planning of therapy in accordance with the degree of the patient's disease.

In a study done by the lymphatic mapping was done using the methylene blue dye and the identification rate of sentinel lymph node was 93.4% (28 patients out of 30).[26] The low identification rate found in several studies could be due to the initial experience of the surgeon, greater BMI of the patients, the obstruction of lymphatics due to the tumour infiltration or the skip metastasis to other nodes such as level III of axilla that contributes to 3.5% to 5% incidence in literature.[27,28] The false negative rate in Sohail et al.[26] was estimated by means of dividing the false negative sentinel lymph node by the total number of the patients who had SLN detected. This was found to be 7.1%. The false negative rate differs among the surgeons between 0 and 15.[29]

In study done by Ozdemir et al, Isosulphane blue or methylene blue was injected in the first method.[30] Radioactive material was injected first, and the sentinel lymph node was found with a gamma probe in another method. This study suggests that these two methods can be used in combination.[31] Methylene blue is associated with the complications such as skin necrosis, fibrosis, and fat necrosis. However, Ozdemir et al reported no such risks while using methylene blue dye.[30]

In the study done by Fattahi et al, the demographic and histopathologic characteristics were not considerably different in patent blue dye group and methylene blue dye group.[32] All the patients had a mean tumour size of 2.4cm with standard deviation of 0.8cm. In the MBD group, the detection rate was found to be 77.5% with MBD only; however, the rate was 94.2% with MBD and radioisotope. In the Patent Blue Dye (PBD) group, the detection rate was found to be 80.1% with dye alone and 92.9% with PBD and radioisotope where $P > 0.05$. The local inflammation was found in one patient in the PBD group and with MBD group, the number of patients with local inflammation was 5 with $P < 0.05$. In a study done by Kasula et al, the findings indicate that the sentinel node is a reasonable predictor of axillary nodal status in the patients with early breast cancer, nevertheless it is

beyond the 5% cut off as suggested by the American Society of Breast Surgeons.[33] By this research, the usage of methylene blue dye was effective in identifying the sentinel node in 86.7% of cases and prior researches with identification rates of sentinel node identification using the methylene blue dye ranging from 83% to 93%.[12,22,34] The remaining patients who did not have dye in the SLN had involvement of these nodes with malignancy and this malignancy also impacted the non-sentinel axillary nodes. When identified successfully, sentinel lymph node biopsy accurately predicts the status of axillary node in 92.3% (12 of 13) and the false negative results in 12.5% (1 of 8). In the study performed by Paulinelli et al, the patients and tumour characteristics were the same in both patient blue and MBD group.[35] About 142 patients were considered for this study. Sentinel lymph nodes were found in 47 patients accounting for 68.1% in PBD group and 43 patients accounting for 60.6% in MBD group with p = 0.35. In PBD group, SLNs were identified in 22 cases (51.2%). In MBD group, the identification was 21 (48.8%) with p = 0.62. In about 12 cases (54.5%), SLN was the only node affected in PBD and in MBD, there were 6 cases (33.3%) with p = 0.18. No complications or allergies reported. In a study by Paulinelli et al.[35], in the patent blue group, the rate of sentinel lymph node detection was 68.1% and in the methylene blue group, the rate of SLN detection was 60.6%.

Comparison of methylene blue with other dyes

The comparison of other dyes with the methylene blue dye in the selected studies is depicted in the table 4. Golshan and Nakhlis state that the methylene blue dye is cheaper compared to Lymphazurin dye.[16] Moreover, methylene blue has no side effects and no allergic or anaphylactic reaction is reported like Lymphazurin hence safer than Lymphazurin. Mathelin et al, state that molecular weight of methylene blue is 319.9 whereas that of Isosulphan blue is 543.[19] These researchers also concur that no allergic reaction is reported with MBD discerning that MBD is safe. Zaazou et al state that with methylene blue dye, the sensitivity and specificity are 88.2% and 86.7% respectively whereas the accuracy, false negative rate, negative predicted value, and rate of metastasis are 95.3%, 11.8%, 92.8%, and 26.5% respectively.[20]

Sohail et al, observe that methylene blue dye has the specificity of 71.4% and sensitivity of 85.7%.[26] The accuracy, false negative, negative predicted value, and positive predicted value are 93.4%, 7.1%, 83.3%, and 75% respectively. Ozdemir et al compare isosulphan with methylene blue.[30] They also observe that methylene blue is cheaper than isosulphan and isosulphan has a hypersensitivity of 0.6% to 2.5%. The accuracy of methylene blue is 92.7% whereas that of isosulphan blue is 88.5%. Fattahi et al, compare methylene blue with patent blue dye wherein the detection rate for methylene blue and patent blue is 77.5% and 80% respectively (dye alone).[32] The detection rate with radiotracer is 94.2% for methylene blue whereas 92.9% for patent blue dye. The methylene blue dye may cause low systemic reaction whereas the patent blue dye can cause anaphylaxis. Kasula et al, found the sensitivity of methylene blue, which was 87.5%.[33] The specificity was 45.45%. The identification rate, accuracy, and negative predicted value for methylene blue dye were 86.7%, 92.3%, and 83.3% respectively. They observe that MBD is an acceptable predictor. The researchers Paulinelli et al, compare three dyes, methylene blue, patent blue, and isosulphan blue.[35] They state that while methylene blue is cheaper, patent blue and isosulphan blue are costlier than MBD.

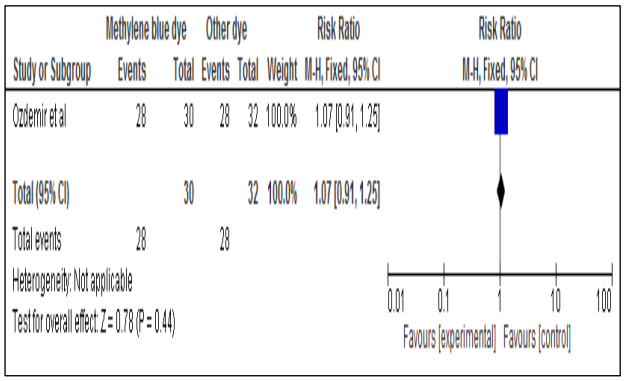

Figure 2: Forest plot of the one included study that quantitatively assessed the accuracy rate between methylene blue dye and other dye.

Figure 2 summarizes the accuracy rate in one study [30]. Heterogeneity tests show that there is no statistically significant heterogeneity between the studies included in the meta-analysis. A summary Risk ratio was found to be 1.07 (95% CI 0.91 to 1.25). The overall test effect for the comparison was Z=0.78 which is lower and not statistically significant (meta-regression, p=0.44>0.05). The findings indicated that there is no statistically significant difference in the accuracy rate among Methylene blue dye and other dye.

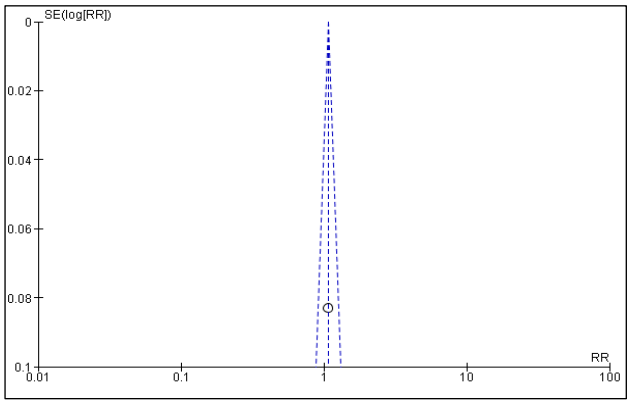

Figure 3: Funnel plot of the one included study that quantitatively assessed the accuracy rate between methylene blue dye and other dye.

A funnel plot (Figure 3) shows that one study were inside the funnel as indicated by the dotted lines.[30] Therefore, it

is concluded that the study did have publication bias as shown in the Figure. This variation in study design might have effect on the findings. The smaller sample size with larger variation is towards the bottom of the funnel while larger studies with less variation are at the top. The overall test effect for the comparison was Z= 0.78 and was not statistically significant (meta-regression, p=0.44).

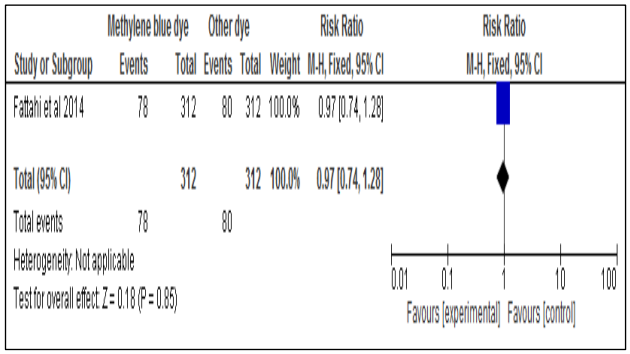

Figure 4: Forest plot of the one included study that quantitatively assessed the detection rate between methylene blue dye and other dye.

Figure 4 summarizes the detection rate in one study.[32] Heterogeneity tests show that there is no statistically significant heterogeneity between the studies included in the meta-analysis. A summary Risk ratio was found to be 0.97 (95% CI 0.74 to 1.28). The overall test effect for the comparison was Z=0.18 which is lower and not statistically significant (meta-regression, p=0.85>0.05). Although the findings indicated that there is no statistically significant difference in the detection rate among Methylene blue dye and other dye.

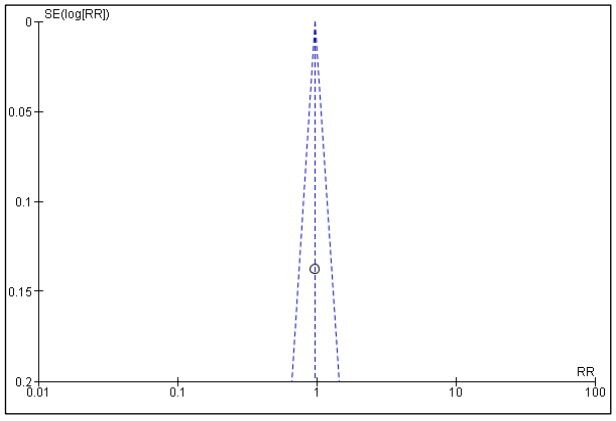

Figure 5: Funnel plot of the one included study that quantitatively assessed the detection rate between methylene blue dye and other dye.

A funnel plot (Figure 5) shows that one study were inside the funnel as indicated by the dotted lines.[32] Therefore, it is concluded that the study did have publication bias as shown in the Figure. This variation in study design might have effect on the findings. The overall test effect for the comparison was Z= 0.18 and was not statistically significant (meta-regression, p=0.85).

Figure 6 summarizes the detection rate with radio tracer in one study.[32] Heterogeneity tests show that there is no statistically significant heterogeneity between the studies included in the meta-analysis. A summary Risk ratio was found to be 1.01 (95% CI 0.80 to 1.28). The overall test effect for the comparison was Z= 0.09 which is lower and not statistically significant (meta-regression, p=0.93>0.05). The findings indicated that there is no statistically significant difference in the detection rate with radio tracer among Methylene blue dye and other dye.

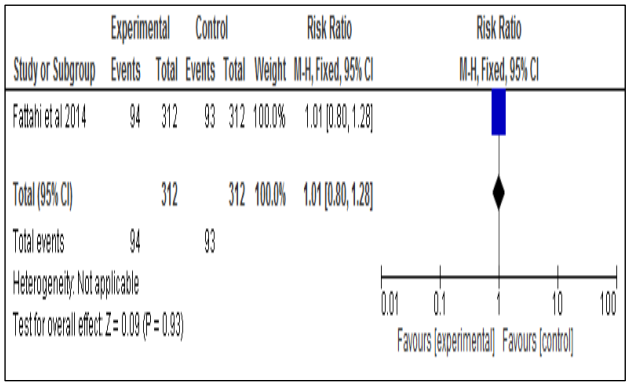

Figure 6: Forest plot of the one included study that quantitatively assessed the detection rate with radio tracer between methylene blue dye and other dye.

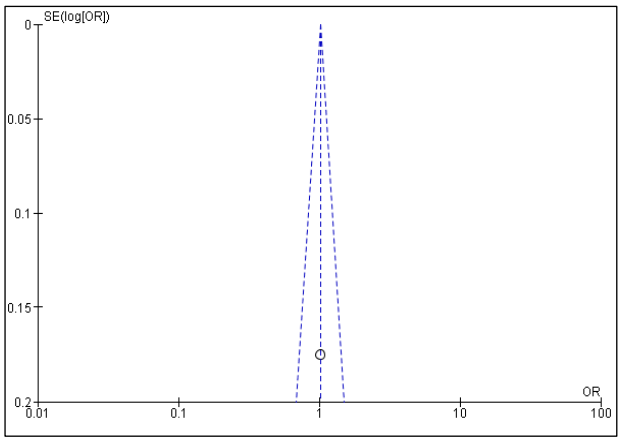

Figure 7: Funnel plot of the one included study that quantitatively assessed the detection rate with radio tracer between methylene blue dye and other dye.

A funnel plot (Figure 7) shows that one study were inside the funnel as indicated by the dotted lines.[32] Therefore, it is concluded that the study did have publication bias as shown in the Figure. This variation in study design might have effect on the findings. The overall test effect for the comparison was Z= 0.09 and was not statistically significant (meta-regression, p=0.93).

Figure 8 summarizes the local inflammation in one study.[32] Heterogeneity tests show that there is no statistically significant heterogeneity between the studies included in the meta-analysis. A summary Risk ratio was found to be 3.00 (95% CI 0.31 to 28.68). The overall test effect for the comparison was Z= 0.95 which is lower and not statistically significant (meta-regression, p=0.34>0.05). The findings indicated that there is no statistically significant difference in the local inflammation among Methylene blue dye and other dye.

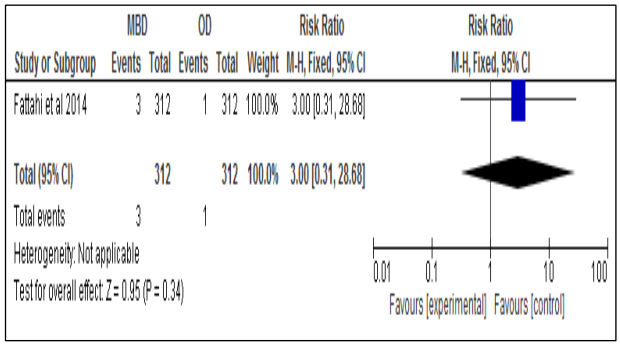

Figure 8: Forest plot of the one included study that quantitatively assessed the local inflammation between methylene blue dye and other dye.

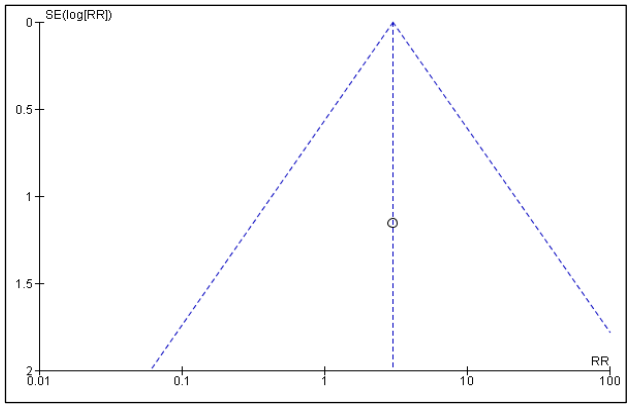

Figure 9: Funnel plot of the one included study that quantitatively assessed the local inflammation between methylene blue dye and other dye.

A funnel plot (Figure 9) shows that one study Fattahi et al.[32] were inside the funnel as indicated by the dotted lines. Therefore, it is concluded that the study did have publication bias as shown in the Figure. This variation in study design might have effect on the findings. The overall test effect for the comparison was Z= 0.95 and was not statistically significant (meta-regression, p=0.34).

Figure 10 summarizes the blue tattooing in one study Fattahi et al.[32] Heterogeneity tests show that there is no statistically significant heterogeneity between the studies included in the meta-analysis. A summary Risk ratio was found to be 0.58 (95% CI 0.31 to 1.11). The overall test effect for the comparison was Z= 1.65 which is lower and not statistically significant (meta-regression, p=0.10>0.05). Although the findings indicated that there is no statistically significant difference in the blue tattooing among Methylene blue dye and other dye.

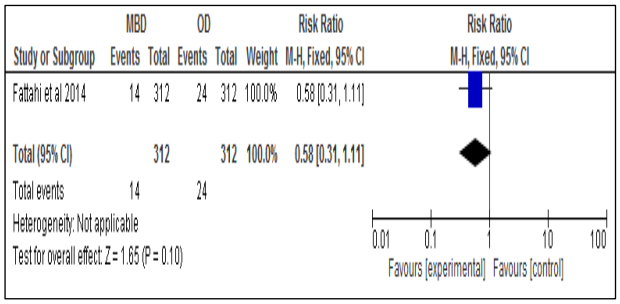

Figure 10: Forest plot of the one included study that quantitatively assessed the blue tattooing between methylene blue dye and other dye.

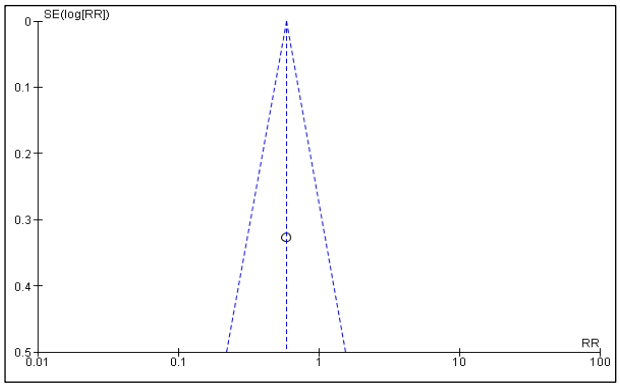

Figure 11: Funnel plot of the one included study that quantitatively assessed the blue tattooing between methylene blue dye and other dye.

A funnel plot (Figure 11) shows that one study Fattahi et al, were inside the funnel as indicated by the dotted lines.[32] Therefore, it is concluded that the study did have publication bias as shown in the Figure. This variation in study design might have effect on the findings. The overall test effect for the comparison was Z= 1.65 and was not statistically significant (meta-regression, p=0.10).

CONCLUSION

A systematic review is done on the utilisation of the methylene blue dye in the sentinel lymph node biopsy in the examination of breast cancer. From the findings of the systematic review, it can be concluded from the information obtained from all the studies for the systematic review and meta- analysis that methylene blue is the best alternative for other dyes in the detection of sentinel lymph node in the case of breast cancer patients using the systematic analysis. Moreover, this dye has lower complication and it is also cheaper and easily available and hence this dye can be used with confidence.

Funding: No funding sources
Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Parasuraman M, Giridharan B, Vijaylakshmi. Use of methylene blue for the detection of sentinel lymph node in breast cancer: a systematic review and meta- analysis. Int Surg J 2018;5:1-10.