

USE OF DYE IN THE PREOPERATIVE MARKING OF NONPALPABLE BREAST LESIONS LITERATURE REVIEW

Uso de corantes na marcação pré-cirúrgica de lesões impalpáveis de mama: revisão de literatura

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ABSTRACT

Objective: To evaluate and compare the use of different dyes in the marking of nonpalpable breast lesions indicated for surgical resection. **Method:** We analyzed the following variables: number of cases, types of dye, technique used for marking (patent blue, indocyanine green, or methylene blue), associated techniques (guidewire or Tc-99m), free margins of the surgical specimen (when the diagnosis was cancer), pain during the marking, and allergic events. The main results of the articles were organized in tables, using the software Microsoft Excel 2011. **Results:** We selected 11 articles for analysis. A total of 510 women had 516 nonpalpable breast lesions marked with dyes. The main dyes used were patent blue, methylene blue, and indocyanine green. The rate of free margins in cancer cases was 95%. Methylene blue was superior to other dyes in obtaining free margins. Out of the 11 articles selected, three associated dye with radioactive materials, and two with guidewire. Two studies analyzed the pain during the marking and revealed that 75% of the patients classified it as moderate or minimal, with mammography being the method most associated with pain. No allergic event was reported. **Conclusion:** The use of dyes in the preoperative marking of nonpalpable breast lesions is a viable, safe, and cheap technique. The initial results of several groups indicate significant advantages compared to the methods currently available. Methylene blue has a lower rate of positive margins than other dyes. Prospective randomized studies are still necessary to verify the superiority of the technique in comparison to others.

KEYWORDS: breast; coloring agents; breast neoplasms; breast cancer.

RESUMO

Objetivo: Avaliar e comparar o uso de diferentes corantes na marcação de lesões não palpáveis de mama que possuem indicação para ressecção cirúrgica. **Método:** Foram analisadas as seguintes variáveis: número de casos, tipos de corante, técnica utilizada na marcação (azul patente, indocianina verde ou azul de metileno), técnicas associadas (fio-guia ou TC-99), margens livres do espécime cirúrgico (quando o diagnóstico era câncer), dor durante a marcação e eventos alérgicos. Organizou-se os principais resultados dos artigos em tabelas, utilizando o programa Microsoft Excel 2011. **Resultados:** Foram selecionados 11 artigos para análise. Ao todo, 510 mulheres realizaram marcação com corantes em 516 lesões impalpáveis de mama. Os principais corantes utilizados foram azul patente, azul de metileno e indocianina verde. A taxa de margens livres em casos de câncer foi de 95%. O azul de metileno foi superior aos demais corantes na obtenção de margens livres. Dos 11 artigos selecionados, em três foi feita a associação do corante com materiais radioativos, e em dois, com o fio guia. A dor durante a marcação foi analisada por dois estudos e classificada como moderada ou mínima por 75% das pacientes, sendo a mamografia o método mais associado à dor. Não foram reportados eventos alérgicos. **Conclusão:** O uso de corantes na marcação pré-operatória de lesões impalpáveis de mama é uma técnica viável, segura e mais barata. Os resultados iniciais de diversos grupos apontam vantagens significativas em relação aos métodos disponíveis atualmente. O azul de metileno apresenta menor taxa de margens comprometidas em relação aos demais corantes. Estudos prospectivos randomizados ainda são necessários para atestar a superioridade da técnica em relação às demais.

PALAVRAS-CHAVE: mama; corantes; neoplasias da mama; câncer de mama.

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INTRODUCTION

The mammography screening for breast cancer has led to an increasing number of diagnoses of nonpalpable breast lesions. The initial approach for nonpalpable lesions with a suspicion of breast cancer must be to perform a core biopsy, fine needle aspiration (FNA), mammotomy, or surgical biopsy. Surgery is indicated when histopathological examination results are inconclusive, the cancer diagnosis is confirmed, or there is disagreement between histological and image findings¹.

The resection of nonpalpable lesions requires the use of preoperative methods to locate them. Ultrasound, mammography, and/or magnetic resonance imaging can be used for injection of radioactive material (radioguided occult lesion localization - ROLL), metallic wire, activated charcoal, or dyes, such as patent blue, methylene blue, and indocyanine green².

We present a literature review on the use of dyes to mark nonpalpable breast lesions indicated for surgical resection.

METHODS

We searched the PubMed, Scientific Electronic Library Online (SciELO), *Biblioteca Regional de Medicina* (Bireme), and Google Scholar databases using the following terms: “nonpalpable breast lesion”; “dyes”; “patent blue”; “indocyanine green”; “methylene blue,” with no language restriction. We included studies that addressed

the preoperative marking of nonpalpable breast lesions using any dye, with or without associated techniques. Two articles were excluded, as their full versions could not be found.

A single author selected the articles based on their abstracts. Next, we read the full versions of the chosen articles. We analyzed the following variables: number of cases, types of dye, technique used for marking (patent blue, indocyanine green, or methylene blue), associated techniques (guidewire or Tc-99m), free margins of the surgical specimen when the diagnosis was cancer, pain during the marking, and allergic events. The main results of the articles were organized in tables, using the software Microsoft Excel 2011.

RESULTS

We selected 11 articles. A total of 510 women had 516 nonpalpable breast lesions marked with dyes. Among the patients with malignant neoplasms, only seven had to be reoperated to enlarge the margins, totaling 4.7% of cases, and 95.3% had free margins (Table 1).

The main dyes used were patent blue, methylene blue, and indocyanine green. Three articles associated dye with ROLL, and two with guidewire. Only one lesion could not be located. After analyzing each dye individually, methylene blue had the best effectiveness in complete lesion resection, and patent blue,

Table 1. Studies using dyes to mark nonpalpable breast lesions and their main results.

Author	Year	Number of patients	Number of lesions	Type of dye	Associated technique	Morphological profile of the resected lesions	Number of cancers	% of positive margins
Vieira et al. ¹	2014	64	64	Patent blue	-	N	13	7.7
Nasrinossadat et al. ²	2011	51	57	Methylene blue	-	N	N	0
Tang et al. ³	2011	78	78	Methylene blue	Injection of Tc-99m	1.2–1.4 cm 39.04–45.18 g	42	0
Liu et al. ⁴	2016	56	56	Indocyanine green	-	38.2±16.5 cm ³	56	5.4
Aydogan et al. ⁵	2012	2	2	Indocyanine green	Injection of Tc-99m	N	2	0
Tang et al. ⁶	2009	138	138	Methylene blue	-	1.2 cm 42 g	84	0
Eulálio Filho et al. ⁷	2016	49	49	Patent blue	-	N	7	0
Pádua Filho et al. ⁸	2004	32	32	Patent blue	-	5.3–3.9 cm	6	50
Zografos et al. ⁹	2003	1	1	Patent blue	Guidewire	N	0	0
Zgajnar et al. ¹⁰	2003	17	17	Patent blue	Injection of Tc-99m	N	17	0
David J ¹³	1989	22	22	Toluidine blue, methylene blue, patent blue	Guidewire	N	N	N

the worst (Table 2). For this analysis, we only included studies in which all patients underwent nodulectomy.

Two studies reported on the pain during the marking and revealed that 75% of the patients classified it as moderate or minimal. The score of pain during the marking performed with ultrasound was 4.68 ± 2.8 , while mammography presented an average of 7.38 ± 1.99 ($p=0.02$). No allergic event was reported.

DISCUSSION

The main dyes used to mark nonpalpable breast lesions are methylene blue, patent blue, and indocyanine green. These dyes, as visual markers, allow the surgeon to excise the lesion and see the areas around the stained tissue to find adequate margins³. Each one has specific characteristics and different costs. The choice of which dye to use is not based on randomized studies.

The excision of nonpalpable breast lesions marked with patent blue was possible in all patients from the published studies. The lesion of one patient was not found because the dye was absorbed before the procedure started. The excision should be performed immediately after applying the dye. Therefore, this failure was attributed to the interval of 100 minutes between applying the dye and beginning the surgery. In this case, the nodule was excised using intraoperative ultrasound. However, in the same study, there are reports of resections of nonpalpable breast lesion done up to 6 hours after marking with patent blue¹, so there must be other variables that may interfere with dye diffusion, such as breast density, injection in the central area of the lesion, or injection inside the ducts, although these data were not analyzed in the published studies.

Indocyanine green has proven to be a promising dye in locating nonpalpable breast lesions, as, after the resection of the area of fluorescence corresponding to the site, the surgical margins were free in 94.8% of 58 cases of breast cancer patients. In addition, it has an excellent safety profile for clinical use. On the other hand, this marker has the disadvantage of requiring a special camera, which increases costs and could limit its use in clinical practice^{4,5}.

A clinical limitation of the methylene blue dye is its rapid diffusion to tissues adjacent to the nonpalpable lesion, defining a greater resection area, which can result in cosmetic defects in the breast. The volume of dye injection might be the main factor

for excessive diffusion. In preliminary studies, approximately 1–2 mL of blue dye were injected, resulting in excessive removal of normal tissues and breast deformity⁶. This issue was solved with the injection of smaller volumes of dye, which currently are around 0.2 mL^{1,7,8}.

Both ROLL and guidewire increase accuracy in the removal of a nonpalpable breast lesion and its safety margin. ROLL was described as the most practical and accurate method to remove a nonpalpable breast lesion. As the radioactive material spreads to adjacent tissues, it defines a safety margin to be excised, thus making the procedure safer and more effective in identifying nonpalpable breast lesions when compared to guidewire. However, this technique requires radioactive material and the joint work of surgeons, nuclear medicine physicians, and radiologists, making it impractical in places that lack medical technological apparatus^{3,5}.

The use of guidewire also has some drawbacks. It is possible to accidentally cut it in the course of the surgery since the wire is thin and flexible, and its end is hard to identify during the procedure¹. Defining the boundaries of the lesion using this technique is also difficult, thus raising the risk of leaving potentially malignant residual lesions or removing a large amount of healthy tissue in an attempt to eliminate the lesion. This explains the worst cosmetic outcome of this technique compared to ROLL^{9,10}. In addition, the guidewire could be displaced, bend, or break. When the wire is sectioned during the surgical act, part of it could remain in the breast parenchyma, which could lead to legal proceedings brought by the patient. If the procedure does not begin with an incision made in the skin puncture site that will receive the metallic wire, locating its tip might be difficult¹. If an incision is made at the puncture site, the procedure will be more invasive and traumatic, particularly for lesions in lower quadrants marked with mammography, as the long path between the entry of the wire and the lesion site will require a larger breast dissection area⁶.

Another interesting technique to mark nonpalpable breast lesions is the use of activated charcoal. The substance is insoluble in water; therefore, it remains in the path, with minimum diffusion to adjacent tissues. It is biologically inert and easily identifiable to the naked eye. These properties give it lower risk of damaging the resected specimen or causing adverse reactions in healthy tissue. Besides, it does not need to be inoculated shortly before the surgery. In a Brazilian study, only 1.48% of the lesions were not located, proving that it can be a safe technique¹¹. Nonetheless, it has major drawbacks not found in dyes, such as the possibility of forming a foreign body or microabscesses, which could harm the histopathological analysis of the tissue^{11,12}.

An important parameter of comparison between preoperative techniques that identify nonpalpable breast lesions is the evaluation of positive margins. Based on data from Table 1, the rate of free margins in neoplasm cases with the use of dyes (methylene blue, fluorescent indocyanine green, toluidine, and patent blue), associated or not with wire or injection of Tc-99m, was 95.3%.

Table 2. Efficiency in localizing the lesion according to the type of dye.

	Number of lesions	Number of cancers	% of positive margins
Patent blue	163	43	9
Methylene blue	273	126	0
Indocyanine green	58	58	5.2

This result shows the high efficiency of dyes in finding the exact location of nonpalpable breast lesions in the preoperative period, allowing total resection, and decreasing the need for reoperation when cancer is diagnosed after surgical resection. Also, this technique has the potential to improve the outcomes according to the surgeon's experience, given that, in 2003, a Brazilian group had 50%⁸ of positive margins; in 2014, this number dropped to 7.7%¹; and, in 2016, all lesions were excised with free margins⁷.

In an evaluation of 56 patients with nonpalpable breast cancer submitted to excision guided by indocyanine green with direct injection of dye into the center of the lesion, aided by ultrasound, 94.6% of cases had satisfactory margins. Two patients with ductal carcinoma *in situ* needed a new excision due to positive margins. One patient (1.8%) required a mastectomy, as she had a multifocal invasive carcinoma, unknown at the time of the first surgery. In this study, the rate of new excision for all procedures was 5.4%, which is comparable to other series that used ultrasound for localization, and better than the one performed with guidewire, which ranged between 6.5 and 21.3%⁴. A Chinese study analyzed 157 patients with nonpalpable breast lesions classified as BI-RADS 5 and revealed that patients marked with dyes had fewer positive margins than those who used guidewire (8 of 42, 19.0% versus 17 of 43, 39.5%, $p=0.038$, respectively)³.

Pain during the marking with the patent blue dye proved to be considerable in a Brazilian study that used an analog scale to assess pain during the procedure. Twelve patients reported mild pain; 25, moderate pain; and 12, intense pain. Marking made with ultrasound had a mean pain score of 4.68 ± 2.8 , while for mammography, this value was 7.38 ± 1.99 ($p=0.02$). Mammography is an uncomfortable procedure due to the compression of the breast parenchyma. This compression lasts longer in the marking with blue dye, which increases the discomfort, justifying the reports from the study. Therefore, marking with ultrasound is the least uncomfortable method for the patient⁷. However, it can only be used on lesions identified by this method. Another study assessed the pain according to the type of dye used, revealing that the injection of toluidine blue caused less discomfort than methylene blue¹³.

An argument against the use of dyes is the possibility of allergic events. In the literature, the incidence of allergic events with patent blue dye ranges from 0.06 to 2.7%¹⁴ and is mainly related to the surgery to detect sentinel lymph node, which uses a higher volume of the substance, usually 2 to 4 mL. The marking of nonpalpable lesions uses only 0.2 mL^{1,7,8}. None of the women marked

with patent blue or other dyes had allergic events. Allergic reactions are rare, but due to their potential risk to life, marking with dyes should be avoided in patients who have allergic history and the procedure should be performed in places with infrastructure for immediate resuscitation in case of anaphylactic shock^{1,11}.

The cost of marking nonpalpable breast lesions with dyes is lower than with guidewire and ROLL, as they do not use nuclear medicine and metallic wires. In Europe, patent blue costs € 8.4. Guidewire increases that value by 4.5 times when placed with ultrasound, while with stereotaxy, it reaches almost 10 times the cost of patent blue. The radioactive isotope used in ROLL costs € 48. When performed with control scintigraphy, that cost increases by € 230, while the marking with patent blue, if made with ultrasound, costs only 3% of this value¹⁴. The marking with methylene blue via ultrasound is available for US\$ 60². These data demonstrate that the use of dyes can be an interesting alternative to reduce the costs of health services in places with scarce financial resources.

Significant differences between the combined technique with an injection of blue dye and guidewire favor the first: reduced rates of re-excision (19 versus 39.5%; $p=0.038$); smaller incisions (mean of 36.3 mm versus 44.8 mm); lower weights of excised specimens (39 g versus 45.2 g); and shorter surgical time (14.7 min versus 16.3 min). In this scenario, the use of dyes is an appealing option, as it can reduce hospital costs and provide good results³.

This review has significant limitations. First, the small number of studies and patients included. Second, the lack of randomized controlled studies. Prospective studies are necessary to determine the best dye to mark nonpalpable breast lesions indicated for surgical resection and what is the real effectiveness of this technique when compared to others.

CONCLUSIONS

The use of dyes in the preoperative marking of nonpalpable breast lesions is a viable, safe, and cheap technique. The rate of free margins in cancer cases was 95% for dyes in general. Individually, methylene blue has the highest efficiency in the localization and proper resection of lesions. The use of ultrasound causes less pain during the marking. The initial results of several groups indicate significant advantages compared to the methods currently available. Prospective randomized studies are still necessary to verify the superiority of the technique in comparison to others.

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