doi: http://dx.doi.org/10.11606/issn.1679-9836.v100i1p35-40 Rev Med (São Paulo). 2021 Jan-Feb;100(1):35-40.

Review Article

The effect of local anesthetic technique on breast cancer-related outcomes: a systematic review

Impacto da técnica anestésica no comportamento evolutivo do câncer de mama: uma revisão sistemática de literatura

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Mussi MCL, Batista AGC, Lucena CEM. The effect of local anesthetic technique on breast cancer-related outcomes: a systematic review / Impacto da técnica anestésica no comportamento evolutivo do câncer de mama: uma revisão sitemática de literatura. Rev Med (São Paulo). 2021 Jan-Feb;100(1):35-40.

ABSTRACT: Although it is an important approach in breast cancer treatment, curative-intent surgery carries a risk of being paradoxically favorable for tumor progression. Since local anesthetic technique is hypothesized as a therapeutic opportunity to reduce neoplastic maintenance and dispersal, we aim to evaluate its effect on breast cancer-related outcomes in the clinical setting. This is a systematic review of the literature that searched for articles in PubMed database using MeSH descriptors: "mastectomy", "mastectomy, radical", "anesthesia, local", "recurrence", "neoplasm recurrence, local". We selected six articles, and the majority of those had a retrospective design, and only one was a randomized controlled trial. Among discussed differences in variables analysis, inclusion criteria and evaluated endpoints, five studies did not present appreciable effect of local anesthetic technique on breast-cancer related outcomes. Thus, although local anesthesia has potential benefits in long-term cancer recurrence and overall survival, this review did not find enough clinical evidence to support this intervention as a standard of practice for such purpose. However, it may reduce intraoperative opioid consumption and provide a feasible option for pain management, that could improve patient's health-related quality of life.

Keywords: Breast neoplasms; Mastectomy; Anesthetics, Local; Neoplasm recurrence; Survival.

RESUMO: Apesar de ser uma importante abordagem para o tratamento do câncer de mama, a cirurgia pode paradoxalmente favorecer a progressão tumoral, apesar da intenção curativa. Como as técnicas de anestesia local podem ser uma oportunidade terapêutica para reduzir a manutenção e dispersão neoplásica, o objetivo do estudo foi avaliar seus efeitos no comportamento evolutivo do câncer de mama no contexto clínico. Trata-se de uma revisão sistemática de literatura a partir da base de dados PubMed com os descritores MeSH "mastectomy", "mastectomy, radical", "anesthesia, local", "recurrence", "neoplasm recurrence, local". Foram selecionados seis artigos, sendo a maioria retrospectivo e apenas um estudo controlado randomizado. Entre as diferenças discutidas na análise de variáveis, critérios de inclusão e resultados observados, cinco estudos não apresentaram efeito sobre o comportamento evolutivo do câncer de mama. Assim, apesar dos potenciais benefícios da anestesia local sobre o comportamento evolutivo do câncer de mama, essa revisão não encontrou evidência suficiente para apoiar essa intervenção para a prática clínica. Apesar disso, pode reduzir o consumo de opioide e prover uma opção viável para o manejo da dor, que pode melhorar a qualidade de vida das pacientes.

Palavras-chave: Revisão sistemática; Câncer de mama; Mastectomia; Anestesia local.

Artigo completo referente a apresentação classificada em 2º lugar na categoria Monograph Award do XXXIX COMU 2020.

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INTRODUCTION

Breast cancer is the most incident cancer in Brazil, except for nonmelanoma skin tumors, with estimated 66,280 new cases for the year of 2020[1]. Worldwide, it is the most incident cancer in women, with estimated 2,100,000 cases and 627,000 deaths in 2018[2].

When multidisciplinary, therapeutic approach of breast cancer increases survival rates and improves patient's quality of life[3]. Although there are continuous advances in treatment options, surgery remains its main support[4].

Surgical removal of the primary tumor occurs with the risk of dispersal of neoplastic cells into the blood and lymphatic systems, as well as the risk of permanence of residual neoplastic cells[5]. Despite curative intent, a combination of perioperative factors leads to a release of chemical mediators that may, paradoxically, be direct or indirectly associated with tumor progression[6].

The surgical stress stablishes a relative immunosuppression, since it activates the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, releasing catecholamines, prostaglandins and growth factors. Prostaglandins and catecholamines may activate beta-2 adrenergic receptors and COX-2, contributing to metastasis establishment[7]. The cytokines release appears to inhibit cell immunity through NK cells, which are important to detect and destroy circulating tumor cells[8]. Furthermore, the surgical tissue trauma stimulates angiogenic factors, like VEGF and TGF, which may increase tumor viability[5].

Local anesthetic technique, as paravertebral thoracic block, attenuates neuroendocrine response to surgical stress and may preserve perioperative immune function[9]. Given that surgical stress response seems to increase opportunities for cancer dissemination and metastasis, this anesthetic approach is hypothesized as beneficial to long-term prognosis[10].

Thereby, we conducted this systematic review to evaluate the effect of local anesthetic technique on breast cancer-related outcomes in the clinical setting.

METHOD

For this present review, the PubMed database was assessed through Mesh descriptors: "mastectomy", "mastectomy, radical", "anesthesia, local", "recurrence", "neoplasm recurrence, local". Reviews, editorials and comments were excluded. The search provided 65 articles, from which 11 were potentially relevant. After integral analysis, 6 studies were selected (Figure 1).

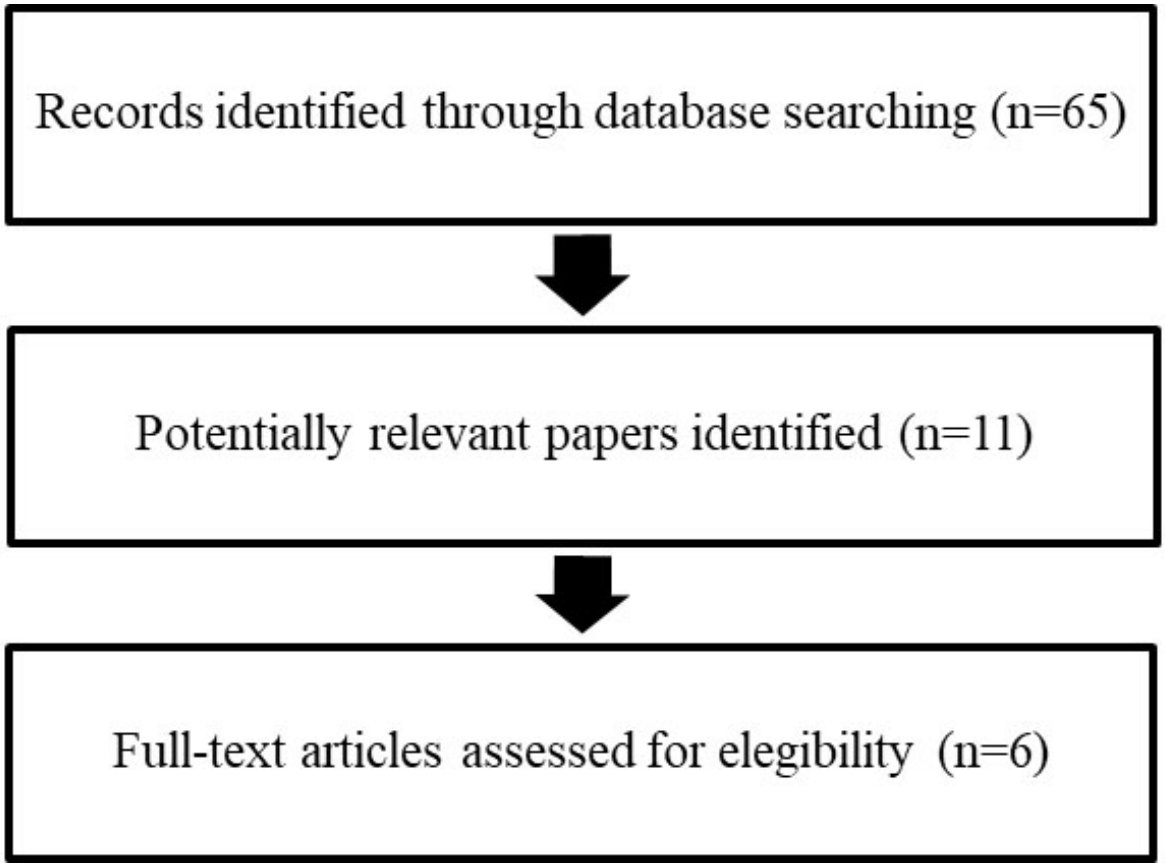

Figure 1. Flow-chart describing the manuscripts' selection process

RESULTS

We found 6 articles, published from 2006[11] to 2019[12], with total samples varying between 129[11] and 2108[12] patients. Of these studies, 4 were retrospective[11,13,14,15], 1 presented a retrospective reviewed of prospective database[16], and only 1 was a multicenter randomized clinical trial[12]. The average observation time varied between 28.8[13] to 72[15] months, and 1 study was stopped after a preplanned futility boundary was crossed[12].

Regarding statistical analysis, 5 articles[11,12,14,15,16] used Cox proportional hazards regression to obtain adjusted results for potential confounding variables that may have influenced the sample prognosis. Furthermore, 2 retrospective studies[14,15] used the Propensity Score Matching (PSM) to establish the samples in order to improve its compatibilities regarding the analyzed variables.

Table 1. Selected articles

Study Autor, year	Study Design	Study groups		Median follow-up time (months)	Measured Outcomes	Statistical measures
		GA	GA + TPVB			
Exadaktylos et al., 2006[11]	RT	79	50	32	RFS	RFS (HR, 0.21 [95% IC, 0.06-0.71]; p=0.012)
Starnes-Ott et al., 2015[13]	RT	193	165	28.8	RFS	RFS (HR, 1.84 [95% CI, 0.34-10.08]; p=0.53)
Tsigonis et al., 2016[14]	RT	375*	375*	66	OS, DFS, LRR	OS (HR, 0.81 [95% CI, 0.59–1.10]; p=0.17) DFS (HR, 0.91 [95% CI, 0.55– 1.76]; p=0.87), LRR (HR, 1.73 [95% CI, 0.83–3.63]; p=0.15).
Cata et al., 2016[15]	RT	198*	198*	69.6 (RFS), 72 (OS)	RFS, OS	RFS (HR, 1.60 [95% CI, 0.81–3.16]; p= 0.172) OS (HR, 1.28 [95% CI, 0.55-3.01]; p=0.567)
Karmakar et al., 2017[16]	PT	58	56 (s-TPVB) 59 (c-TPVB)	60	LRR, OS	GA + s-TPVB LRR (HR, 1.11 [95% CI, 0.32-3.83]; p=0.88), GA + c-TPVB LRR (HR, 0.79 [95% CI, 0.21-2.96]; p=0.88) GA + s-TPVB OS (HR, 2.57 [95% CI, 0.66-9.92]; p=0.15) GA + c-TPVB OS (HR, 0.66 [95% CI, 0.11-3.97]; p=0.15)
Sessler et al., 2019[12]	RCT	1065	1043	36	LRR	LRR (HR, 0.97 [95% CI, 0.74-1.28]; p=0.84)

GA: General Anesthesia; TPVB: Thoracic Paravertebral Block; RT: retrospective; RFS: recurrence-free survival; HR: hazard ratio; OS: overall survival; DFS: disease-free survival; LRR: local regional recurrence; PT: prospective; s-TPVB: single TPVB injection followed by 72h postoperative placebo infusion; c-TPVB: continuous TPVB infusion 72h after surgery; RCT: randomized controlled trial *Sample obtained after PSM.

The first study was published in 2006 by Exadaktylos et al.[11], that provided a retrospective analysis of 129 patients with a palpable breast lesion who underwent a mastectomy with axillary clearance or simple complete mastectomy. Patients with screen-detected cancer and those having plastic or reconstructive surgery were excluded. It was found a rate of recurrence-free survival in the GA + TPVB and GA groups as, respectively, 94% (95% CI, 87-100) and 82% (95% CI, 74-91) for 24 months, and 94% (95% CI, 87-100) and 77% (95% CI, 68-87) for 36 months (p=0.012).

No significative differences between the patient features, surgical details or prognostic factors were reported. However, the Nottingham prognostic index (that involves tumor size, axillary lymph node involvement, and histological grade), used in this study, is not validated to measure recurrence and metastasis propension[17]. Furthermore, it did not consider obesity as a variable that may have influenced medical decision in using general anesthesia[13], aside from being considered a potential risk factor for tumor recurrence[18]. However, the promising result stimulated further clinical studies.

Starnes-Ott et al.[13] selected stage 0-III breast cancer patients submitted to partial or radical mastectomy, with or without lymph node dissection. The groups significatively varied in body mass index (BMI), and those in the GA group had a higher BMI than the GA+TPVB group (p=0.001). Also, patients in the GA+TPVB group were in more advanced stages (II or III) than the control group (p=0.01), were more submitted to chemotherapy (p=0.02) and had slightly longer surgical procedures (p=0.01). In the average period of 28.8 months observation time, the recurrence rate in the GA group was 1.4 per 100 000 person-days, and in the GA+TPVB group it was 2.6 per 100 000 person-days. The small number of events did not permit the analysis through adjusted variables.

Tsigonis et al.[14] retrospectively review a prospective database of women stage 0-III breast cancer, not submitted to neoadjuvant therapy or 'flap' reconstruction. Patients from the TPVB group were older and had smaller, low staged and more hormone receptor-positive tumors. After using PSM to make the groups more comparable, except for tumor stage (p=0.026), there was no statistical difference between the groups for the evaluated outcomes.

The retrospective analysis made by Cata et al.[15]

evaluated women submitted to mastectomy with or without axillary lymph node dissection for non-metastatic cancer. After adjustment of variables, the analysis did not associate TPVB with significant change in measured outcomes. However, there was a substantial reduction in the intraoperative consumption of opioid. While the GA group received 541.06 ± 498.07 μg, the GA + TPVB group received 122.8 ± 77.85 μg in fentanyl equivalents ($p < 0.001$).

The intraoperative opioids usage was also analyzed by Karmakar et al.[16], that used the same cohort to also assess chronic pain and health-related quality of life[19]. It was included women ASA 1-3, aged less than 70 years old, submitted to mastectomy with lymph node dissection. Since chronic pain was also assessed, women with previous chronic diseases or history of chronic pain were excluded. The GA + TVPB group was divided in two: one received a single ropivacaine injection associated to the GA, followed by a continuous saline infusion in the post-operative period (s-TPVB), and other that received a continuous ropivacaine infusion in the 72h post-operative period (c-TPVB). The measured outcomes were not significative different among the 3 groups. However, the intraoperative opioid medication was higher in the GA group [1.5 (IQR=0-3) mg] when compared to s-TPVB [0 (IQR=0–1) mg] ($p<0.001$) and c-TPVB [0 (IQR=0-1) mg] ($p=0.001$) groups.

The authors also reported that there was no significant difference in the incidence or relative risk of chronic pain when TPVB is associated with GA. However, TPVB groups presented lower pain intensity ($p<0.05$), fewer signs and symptoms of chronic pain ($p\leq0.01$), and a better physical and mental health when compared to the GA group[19].

The only randomized clinical trial was realized by Sessler et al.[12] at 13 hospitals, in Argentina, Austria, Germany, Ireland, New Zealand, Singapore, United States and China, country that accounted for 59% of the sample. Women under 85 years old, diagnosed with primary breast cancer, with or without lymph node involvement, scheduled for unilateral or bilateral mastectomy were randomized. Women with previous breast cancer surgery, inflammatory carcinoma, ASA ≥4, who were scheduled for free-flap reconstruction or had the anesthetic approach contraindicated were not included. Among the GA+TPVB group, there was 102 (10%) recurrences, compared to 111 (10%) of the GA group (HR, 0.97 [95% CI, 0.74-1.28]; $p=0.84$). Incisional pain after six months was reported by 442 (52%) of 856 patients from the GA+TPVB group and by 456 (52%) of 872 patients from the GA group; after 12 months, it was reported by 239 (28%) of 854 patients from GA+TPVB group and by 232 (27%) of 852 patients from GA group (overall interim-adjusted odds ratio 1,00, 95% CI 0·85–1·17; $p=0.99$). This study did not show difference between the anesthetic groups in terms of cancer-outcomes and frequency and severity of persistent incisional breast pain.

DISCUSSION

The results of retrospective studies, as the majority of our selection, are conditioned to the accuracy and availability of the information. Also, the assessment of predetermined variables and results of interest may be influenced by unmeasured factors, that could be confounding. Examples as the consumption of beta-blockers[20] and non-steroidal anti-inflammatory drugs[21], as well as postoperative wound complications[22], are also studied as possible interfering factors for breast cancer-related outcomes during the perioperative period and were not observed as variables in our selected studies.

Anesthetic agents could also have impact on tumor progression. Propofol, used in three clinical studies[11,12,16], reduced in vitro expression of Neuroepithelial Cell Transforming Gene 1, NET1, that promotes the migration of breast adenocarcinoma cells lines[23]. In vivo, propofol maintained the activity of NK cells and avoided pulmonary metastasis in animal models with breast neoplastic cells[24].

Although there is not an actual consensus in literature regarding the type, dosage and application site, the use of intraoperative opioids as adjuvant drug for pain management also seems to present immunomodulatory effects that may impact cancer-related outcomes. One laboratorial study using breast neoplastic cells indicated higher activity of NK and T helper cells in models that received propofol and paravertebral anesthesia when compared to general anesthesia with opioid analgesia[25]. Also, it is considered that thoracic paravertebral block reduces the administration of perioperative opioids[26], as observed by Sessler et al.[12], that indicated a reduction in intraoperative morphine consumption with a standardized absolute difference of 1.8 between GA and GA+TPVB groups.

TPVB is a feasible therapeutic approach to reduce postoperative pain in breast cancer treatment, becoming a relevant intervention to facilitate recovery, accelerate hospital discharge and reduce care costs after the surgery[27], considering that chronic pain is a common complaint for these patients[28]. Both studies that assessed chronic pain[12,19] have not found reduction in chronic pain incidence, however, Karmakar et al.[19] observed less pain intensity in the GA + TPVB group.

CONCLUSION

Although preclinical studies suggested potential benefits of local anesthesia to reduce cancer recurrence and improve overall survival, this review did not find enough clinical evidence to support thoracic paravertebral block for this purpose in breast cancer surgery. However, local anesthesia may impact the reduction of intraoperative opioid and support pain management in the postoperative period, potentially improving patient's health-related quality of life.

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Received: 2020, November 17
Accepted: 2021, February 04