ORIGINAL ARTICLE

Impact of Regional Anesthesia on Recurrence, Metastasis, and Immune Response in Breast Cancer Surgery

A Systematic Review of the Literature

Oscar Pérez-González, MD,†‡ Luis F. Cuéllar-Guzmán, MD,*‡ José Soliz, MD,§ and Juan P. Cata, MD‡§*

Background and Objectives: The perioperative period is critical in the long-term prognosis of breast cancer patients. The use of regional anesthesia, such as paravertebral block (PVB), could be associated with improvements in long-term survival after breast cancer surgery by modulating the inflammatory and immune response associated with the surgical trauma, reducing opioid and general anesthetic consumption, and promoting cancer cells death by a direct effect of local anesthetics.

Methods: A systematic literature search was conducted for studies of patients who received PVB for breast cancer surgery. The Jadad score and Ottawa-Newcastle scale were used to assess the methodological quality of randomized controlled trial and observational retrospective studies, respectively. Only high-quality studies were considered for meta-analysis. The selected studies were divided into 3 groups to determine the impact of PVB on (*a*) recurrence and survival, (*b*) humoral response, and (*c*) cellular immune response.

Results: We identified 467 relevant studies; 121 of them underwent title and abstract review, 107 were excluded, and 15 studies were selected for full text reading and quality assessment. A meta-analysis was not conducted because of low-quality studies and lack of uniform definition among primary outcomes. Thus, a systematic review of the current evidence was performed.

Conclusions: Our study indicates that there are no data to support or refute the use of PVB for reduction of cancer recurrence or improvement in cancer-related survival. However, PVB use is associated with lower levels of inflammation and a better immune response in comparison with general anesthesia and opioid-based analgesia.

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Breast cancer is the second most common among all cancers, ranking also as the fifth cause of death among cancer overall.[1] Metastatic recurrence is the main cause of breast cancer–related deaths. It is estimated that 30% to 40% of patients will die of metastatic disease, despite surgical removal of the primary tumor, chemotherapy, and radiotherapy.[2]

Surgery remains as the cornerstone therapy for a large number of patients with breast cancer. The perioperative period is critical in the long-term prognosis of breast cancer patients. Several experimental studies have suggested that the stress response associated with surgical trauma may promote the proliferation of breast cancer cells that are part of the minimal residual disease.[3–5] Other factors, such as anesthetic drugs, type of anesthesia technique, acute pain, and opioids, have also been implicated in the metastatic process.[6–9] Thus, it was hypothesized that the use of a regional anesthesia technique, such as the paravertebral block (PVB), could be associated with improvements in long-term survival after breast cancer surgery.[10] The proposed mechanisms include the modulatory effects of regional anesthesia on the inflammatory and immune response associated with the surgical trauma, sparing opioid and general anesthetic effects, a potential direct antitumor effect of local anesthetics on cancer, and protective effects on innate immune cells.[10,11]

The aim of this study was to conduct a systematic review and meta-analysis to assess the impact that regional anesthesia, specifically PVBs, had on biological markers of inflammation, immunosuppression, and angiogenesis during breast cancer surgery. We also investigated the implications of PVBs on clinical outcomes including recurrence, recurrence-free survival (RFS), and overall survival (OS).

METHODS

Literature Search Strategy

A systematic literature search of PubMed, EMBASE, MEDLINE, the Cochrane Trials Register, and Web of Science databases was conducted. Each database was searched separately by one of the authors (O.P.-G.). These databases were searched from inception through December 2017. The strategy used included methods of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[12] Search terms included combinations of MeSH (Medical Subject Headings): "Breast Cancer" or "Anesthetic Technique" or "Anesthesia" or "Epidural Anesthesia" or "Regional Anesthesia" or "Epidural Analgesia" or "Disease Free Survival" or "Progression Free Survival" or "Recurrence" or "Metastasis. Additional filters were added, such as "Randomized Controlled Trials," "Controlled Trials," "Human." Bibliographies of retrieved studies were also examined. To help ensure no cancer recurrence records were missed, survival and metastasis-related search terms were added to the search strategies.

Inclusion and Exclusion of Trials

Inclusion criteria for studies were (*a*) randomized controlled trials (RCTs) and observational cohort studies published in English language, (*b*) studies including adult patients, (*c*) reports including patients undergoing breast cancer surgery, (*d*) publications including any regional anesthesia technique for breast cancer surgery, and (*e*) studies assessing the effects of regional anesthesia or analgesia on postoperative outcomes including humoral and cellular markers of inflammation and immune function, cancer recurrence rate, RFS, disease-free survival (DFS), cancer-specific survival,

From the *Department of Anesthesiology and Intensive Care, National Cancer Institute, Mexico City; and †Department of Anesthesiology, Cancún General Hospital, Quintana Roo Health State Services, Cancún, Mexico; and ‡Anesthesiology and Surgical Oncology Research Group; and §Department of Anesthesiology and Perioperative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX.

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Address correspondence to: Juan P. Cata, MD, Department of Anesthesiology and Perioperative Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 409, Houston, TX 77005 (e-mail: jcata@mdanderson.org).

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and/or OS. Exclusion criteria were (*a*) in vitro and animal studies and (*b*) case reports.

Selection of Studies and Quality Assessment

Two authors (J.P.C. and O.P.-G.) independently assessed titles and abstracts for inclusion in the systematic review. Any disagreements between the 2 reviewers were resolved by a third author (L. F.C.-G.). The Jadad score (Oxford Quality Scoring System, http://www.pmidcalc.org/index.php) was used to adequately assess the methodological quality of RCTs. The Newcastle-Ottawa scale was used to grade the quality of observational retrospective studies.[13] Only studies graded as high quality (ie, Jadad score ≥3 or Newcastle-Ottawa score ≥8) were considered for inclusion in the meta-analysis.

RESULTS

Our initial search identified 467 article; 121 of them were eligible for title and abstract review. One hundred and seven manuscripts were excluded, and 15 studies were selected for full text reading and quality assessment (Fig. 1).

Association Between PVB Analgesia and Cancer-Related and Overall Survival

A total of 6 studies (Table 1) investigated the association between PVB/general anesthesia (GA) and volatile GA/opioid-based anesthesia/analgesia on cancer recurrence rates, RFS, cancer-specific survival, and OS. Except 1 study, all of the aforementioned studies were retrospective and included sample sizes ranging from 60 to 1107 patients. The only published RCT showed no difference in the rate of recurrence between patients who had PVB versus placebo.[18] Among the retrospective studies, 1 study showed a beneficial effect of PVB, 1 study showed a negative impact on PVB, and the remainder found no association between the use of PVB and a reduced rate of cancer recurrence or longer cancer-related survival.[10,14,15,17] A meta-analysis was not conducted because of (*a*) low-quality studies, (*b*) different staging and molecular tumor markers in the patients included in each study, (*c*) different solutions of local anesthetics used for PVB, and (*d*) differences in outcome definitions.

Impact of PVB Analgesia on Biomarkers

Four RCTs (Table 2) investigated the impact of PVB in combination with propofol GA versus volatile GA and opioid analgesia on markers of inflammation, immune response, and angiogenesis. A meta-analysis was not performed because of (*a*) low-quality studies and (*b*) high heterogeneity in type and time of cytokine measurements.

Impact of PVB Analgesia on Cell Immune Responses and Cancer Cell Function

Four RCTs studied the effect of PVB/propofol GA versus volatile GA and opioid-based analgesia on breast cancer cell proliferation, apoptosis, immune cell infiltration (CD56+, CD4+, CD8+ and CD68+ cells) at tumor level, and peripheral natural killer (NK) cell function (Table 3). A meta-analysis could not be conducted because of (*a*) low-quality studies and (*b*) high heterogeneity among studies.

DISCUSSION

Our study has found that the level of evidence regarding the impact of regional anesthesia on survival outcomes after breast cancer surgery is low. Only 1 RCT has tested the hypothesis that

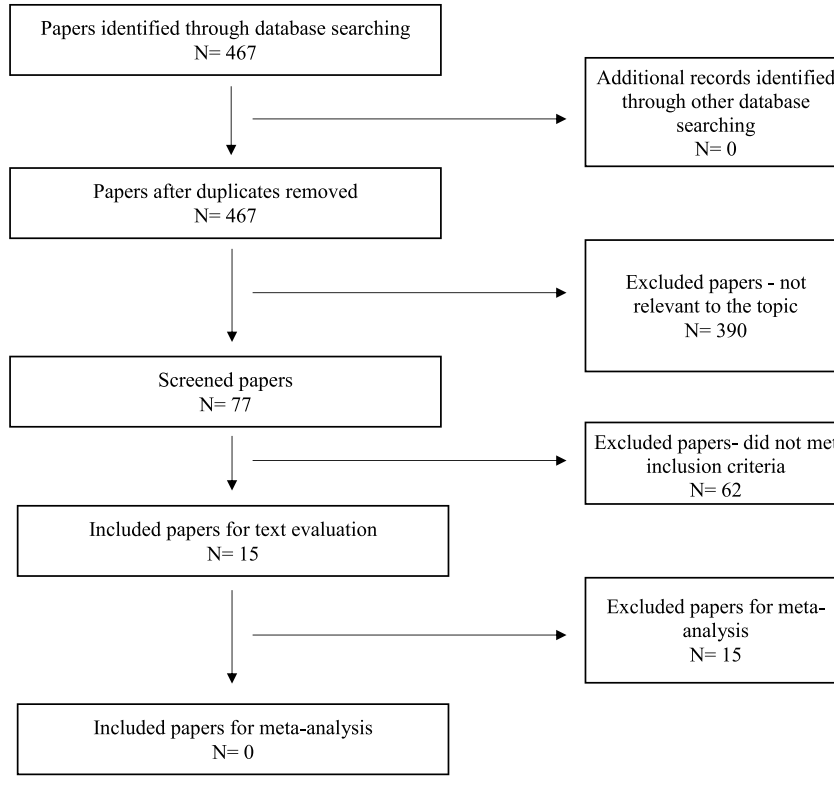

FIGURE 1. Preferred Reporting Items for Systematic Review and Meta-analysis Protocols flowchart.

TABLE 1. Summary of Clinical Studies That Analyzed the Impact of PVB on Breast Cancer Recurrence or Survival

Study (Author, Year)	Study Design	Intervention	Dose, Treatment Duration, Plasma Concentrations	RA Group, n	GA Group, n	Measured Outcome	Follow-Up Time, y	Notes	Ottawa-Newcastle or Jadad Score
Exadaktylos et al[10] (2006)	Retrospective	Thoracic PVB (levobupivacaine 0.2%)/ propofol vs GA (sevoflurane + opioid)	2 mL/kg 48 h NR	50	79	Incidence of metastatic spread	2.5 ± 0.4	PVB was associated with lower rate of recurrence	7
Starnes-Ott et al[14] (2015)	Retrospective	PVB (ropivacaine 1%, clonidine 100–150 μg, epinephrine 1:400,000) + GA vs GA (volatile anesthetic + opioid)	NR Single bolus NR	193	165	Recurrence rate, RFS	2.4	No significant association between anesthesia type and recurrence was observed	7
Kairaluoma et al[15] (2016)	Retrospective	Thoracic PVB bupivacaine 1.5 mg/kg + GA sevoflurane vs sham block + GA sevoflurane	1.5 mg/kg Single bolus 1.7 ± 0.7 mM	45	41	DFS, DRFS, BCSS, OS	1, 5, 10, and 12	No association between type of anesthesia DFS, DRFS, BCSS, or longer OS in PVB group	7
Tsigonis et al[16] (2016)	Retrospective review of prospective database	Stage 0–III breast cancer, 9 y preceding January 1, 2010	NR Single bolus NR	646	461	OS, DFS, LRR	5.5 to 12.5	No impact on main outcomes first comparison of cancer outcomes in breast cancer patients stratified by avoidance of GA and inclusion of patients undergoing breast-conserving therapy	8
Cata et al[17] (2016)	Retrospective PSM	Thoracic PVB (ropivacaine 1%, clonidine 100–150 μg, epinephrine 1:400,000) vs GA (volatile anesthetic + opioid)	3–4 mL per level Single bolus NR	197	197	RFS, OS, Recurrence rate	5.7 - 6.2	No association between type of anesthesia and survival	8
Finn et al[18] (2017)	RCT	Thoracic PVB (ropivacaine 0.4%) vs placebo (normal saline)	5 mL/h 72 h NR	26	28	Cancer recurrence rates	2	No difference in cancer recurrence rates between groups	2

BCSS indicates breast cancer–specific survival; DRFS, disease recurrence-free survival; LRR, local regional recurrence; NR, not reported; OQSS, Oxford Quality Scoring System; PSM, propensity score matching; RA, regional anesthesia; RI, Recurrence Index.

TABLE 2. Impact of PVB Analgesia on Biological Markers

Study (Author, Year)	Study Design	Intervention	Dose, Treatment Duration, Plasma Concentrations	RA Group, n	GA Group, n	Measured Outcome	Follow-Up Time	Results	Jadad Score
O'Riain et al[19] (2005)	RCT	PVB (bupivacaine 0.25%) + GA vs GA + opioid	15-mL bolus 10 mL/h 48 h NR	15	15	Glucose, cortisol, VEGF, PGE_2, CRP	Preoperative and 4 to 24 h postoperative	Reduction of the stress response in the PVB + GA group, but no significant changes in VEGF and PGE_2	−1
Looney et al[20] (2010)	RCT	PVB (levobupivacaine 0.25%) + propofol vs GA (sevoflurane) + opioid	20-mL bolus 8–10 mL/h 48 h NR	20	20	VEGF-C and TGF-β	Preoperative and 24 h postoperative	Anesthetic technique may reduce risk of metastasis in early breast cancer by TGF-β modulation	1
Deegan et al[21] (2010)	RCT	PVB (bupivacaine 0.25%) + propofol vs GA (sevoflurane) + opioid	20-mL bolus 8–10 mL/h 48 h NR	15	17	11 Cytokines and 3 MMPs level after different anesthetic regimen	Preoperative and 24 h postoperative	PVB + GA reduced IL-1B, MMP-3, and MMP-9 and increased IL-10	2
Sultan[22] (2013)	RCT	PVB (bupivacaine 0.5%) + propofol vs GA (sevoflurane) + opioid	5-mL bolus NR NR	NR	NR	IL-6, IL-10, IL-12, IFN-γ, IFN-γ/IL-10	No follow-up reported	PVB group showed attenuation in cytokine response to surgery	−1

IFN indicates interferon; NR, not reported; PGE_2, prostaglandin E_2; RA, regional anesthesia; TGF-β, Transforming growth factor β; VEGF, vascular endothelial growth factor.

TABLE 3. Summary of Studies Addressing the Role of Type of Anesthesia on Immune- and Cancer-Related Parameters After Breast Cancer Surgery

Study (Author, Year)	Study Design	Intervention	Dose, Treatment Duration, Plasma Concentrations	RA Group, n	GA Group, n	Measured Outcome (In Vitro)	Notes	Jadad Score
Deegan et al[23] (2009)	Pilot RCT	PVB (levobupivacaine 0.25%) + propofol vs GA (sevoflurane + opioid)	20-mL bolus 8–10 mL/h 48 h	11	11	MDA-MB-231 ER-negative cell proliferation	MDA-MB-231 significantly reduced in PPA group, but no significant change in cell migration between groups	1
Desmond et al[24] (2015)	RCT	PVB vs GA	NR NR NR	12	16	Immune cell infiltration (CD56, CD4, CD8, CD68) breast cancer tissue	PVB increased NK and T-helper cell infiltration into breast cancer tissue	2
Buckley et al[30] (2014)	Pilot RCT	PVB (levobupivacaine 0.25%) + propofol vs GA (sevoflurane + opioid)	20-mL bolus 8–10 mL/h 48 h	5	5	NK markers of degranulation and activation	PPA preserved NK cell activity compared with GA	1
Jaura et al[25] (2014)	Pilot RCT	PVB (levobupivacaine 0.25%) vs GA (sevoflurane + opioid)	20-mL bolus 5–10 mL/h 48 h	10	10	Apoptosis in ER-negative MDA-MB-231 breast cancer cells	Apoptosis of MDA-MB-231 cancer cells was significantly reduced in SGA group; cancer cell viability was similar in both groups	1

ER indicates estrogen receptor; PPA, propofol-PVB anesthesia; RA, regional anesthesia; SGA, sevoflurane general anesthesia.

PVB reduces the rate of recurrence after breast cancer surgery; however, it is worth mentioning that the study was inadequately powered. Thus, interpretation of its results should be taken with extreme caution.[18] In 2006, Exadaktylos et al[10] showed that women receiving a combination of PVB and propofol GA had slower times to recurrence than did those having GA with sevoflurane and opioids. In that study, the rate of recurrence was 6% in patients in the PVB/propofol group versus 24% in those in the sevoflurane/opioid anesthesia group.[10] After adjusting for significant variables, the use PVB/propofol was associated with significant reduction in the risk of cancer recurrence ($P = 0.012$; hazard ratio, 0.21 [95% confidence interval, 0.06–0.71]).[10] In striking contrast, Kairaluoma et al[15] reported a significant improvement in OS but not in DFS, disease RFS, and breast cancer–specific survival in women who received a PVB in combination with sevoflurane GA in comparison to those treated with a sham block in combination with sevoflurane GA. In that study, the OS rates at 12 years were 92.6% and 73.7% ($P = 0.035$) in the PVB group and sham group, respectively.

No association between the type of anesthesia technique and improvement in survival was observed in 3 different studies. Starnes-Ott et al[14] found that the recurrence rate in the volatile GA-opioid group was 1.4 per 100 000 person-days and 2.6 per 100 000 person-days in the PVB-GA group. In agreement with that study, Tsigonis et al[16] concluded that the OS, DFS, and local regional recurrence were not significantly different between women who received GA or local regional anesthesia. Lastly, Cata et al[17] showed similar RFS and OS estimates in women with and without PVB, despite demonstrating a significant reduction in the use of opioids on the PVB group. In that study, the mortality rate was slightly higher in the PVB group (n = 13 [6.57%]) than in the non-PVB group (n = 30 [5.05%]), but it did not reach statistical significance ($P = 0.415$).[17] It is important to highlight that all the studies included in our review of regional anesthesia and impact on cancer survival outcomes have significant limitations including (*a*) retrospective design, selection bias, and different statistical analysis; (*b*) heterogeneity in type of anesthetic technique; and (*c*) lack of accurate information on tumor size, staging, presence of mutations, and type or completion of neoadjuvant or adjuvant treatment (ie, chemotherapy and radiation).[26]

It has been hypothesized that one of the mechanisms by which regional anesthesia may decrease cancer recurrence is through an anti-inflammatory effect and reduction of the surgical stress response.[27] Three of the RCTs included in our systematic review assessed the effect of PVB on several circulating inflammatory and anti-inflammatory cytokines, prostaglandin E_2, cortisol, C-reactive protein, and matrix metalloproteinases (MMPs). Overall, the studies found a small to modest reduction in inflammatory biomarkers (ie, interleukin 1 [IL-1], IL-6, MMP-3, and MMP-9) and markers of the stress response (ie, serum cortisol, serum glucose, and C-reactive protein) in patients who received a PVB.[19,21,22] The same studies could not demonstrate any significant difference in the concentrations of circulating anti-inflammatory such as IL-10.[21,22] The impact of PVB on the serum concentrations of cytokines with predominant antitumor effects such as interferon, IL-2, and IL-12 was less clear. Whereas Sultan[22] found that women with a PVB had higher circulating concentrations of interferon than did those without a block, Deegan et al[21] observed no change in the concentrations of that cytokine.[21,22]

A second mechanism by which regional anesthesia may improve the survival of patients after breast cancer surgery is through a reduction in the concentrations of growth factors with proliferative or angiogenesis effects. Two RCTs compared the postoperative concentrations of vascular endothelial growth factor (VEGF) in women who received PVB/propofol GA and those treated with sevoflurane/opioid GA. In a different study, O'Riain et al[19] found that the type of anesthesia technique did not impact the postoperative concentrations of VEGF. Lastly, Jaura et al[25] and Deegan et al[23] investigated whether the in vitro exposure of breast cancer cells to the serum of women who had breast cancer surgery with or without regional anesthesia had any effect on proliferation and apoptosis. The main findings of these studies were an antiapoptotic effect mediated by the serum of women who received sevoflurane/opioid GA and inhibition of cell proliferation after the exposure to serum of women who had PVB/propofol GA.[23,25]

Women who receive general volatile anesthesia show a significant decrease in the count and function of NK cells.[28,29] Therefore, it has been hypothesized that regional anesthesia could ameliorate the suppressive effect that surgery per se, volatile anesthetics, and opioids have on those cells. Two RCTs have demonstrated that women who underwent mastectomies and were treated with PVB/propofol GA showed not only a better preservation of in vitro NK cell function but also a higher intensity of $CD56^+$ cells in the tumor microenviroment in comparison to women who had GA with sevoflurane and opioids.[24,30]

In conclusion, the current data do not support or refute the use of PVB for reduction of cancer recurrence or improvement in cancer-related survival. Although the data suggest that PVB may decrease perioperative inflammation and prevent immune suppression and diminish angiogenesis, further evidence is required because we found that in most studies PVBs were used in combination with propofol (an anesthetic with anti-inflammatory effects and anti-invasive properties in cancer cells).[31] A large RCT (NCT00418457) is currently enrolling patients with stage 1 to stage 3 breast cancer. Patients are randomly assigned to thoracic epidural or paravertebral anesthesia/analgesia or to GA and opioid analgesia. It is expected that recruiting will finish in 2019.

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