Review Article

Can Acute Pain Treatment Reduce Postsurgical Comorbidity after Breast Cancer Surgery? A Literature Review

Fumimasa Amaya,1 Toyoshi Hosokawa,2 Akiko Okamoto,2,3 Megumi Matsuda,1 Yosuke Yamaguchi,1 Shunsuke Yamakita,1 Tetsuya Taguchi,3 and Teiji Sawa1

1Department of Anesthesiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kajiicho 465, Kamigyoku, Kyoto 6020841, Japan
2Department of Pain Management and Palliative Care Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kajiicho 465, Kamigyoku, Kyoto 6020841, Japan
3Department of Endocrinological and Breast Surgery, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kajiicho 465, Kamigyoku, Kyoto 6020841, Japan

Correspondence should be addressed to Fumimasa Amaya; ama@koto.kpu-m.ac.jp

Received 16 April 2015; Revised 25 August 2015; Accepted 3 September 2015

Academic Editor: Chi Wai Cheung

Copyright © 2015 Fumimasa Amaya et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Regional analgesia, opioids, and several oral analgesics are commonly used for the treatment of acute pain after breast cancer surgery. While all of these treatments can suppress the acute postsurgical pain, there is growing evidence that suggests that the postsurgical comorbidity will differ in accordance with the type of analgesic used during the surgery. Our current study reviewed the effect of analgesics used for acute pain treatments on the major comorbidities that occur after breast cancer surgery. A considerable number of clinical studies have been performed to investigate the relationship between the acute analgesic regimen and common comorbidities, including inadequate quality of recovery after the surgery, persistent postsurgical pain, and cancer recurrence. Previous studies have shown that the choice of the analgesic modality does affect the postsurgical comorbidity. In general, the use of regional analgesics has a beneficial effect on the occurrence of comorbidity. In order to determine the best analgesic choice after breast cancer surgery, prospective studies that are based on a clear definition of the comorbidity state will need to be undertaken in the future.

1. Background

Breast cancer surgery is a common surgical procedure performed throughout the world. American Cancer Society estimated that, in the United States, there are more than 2.8 million breast cancer survivors [1]. Acute postsurgical pain commonly exists after the breast cancer surgery. Katz et al. demonstrated that 54% of the patients who received breast cancer surgery experienced clinically meaningful pain (defined as worst pain intensity larger than or equal to 5 in 0–10 numerical rating scale) [2]. Postsurgical pain can be affected by the surgical procedure. Breast reconstruction is associated with severe and long lasting postsurgical pain [3, 4]. Abnormal sensation is less frequent in sentinel lymph node biopsy compared to the axillary lymph node dissection immediately after the surgery and up to 5 years thereafter [5]. Healthcare problems frequently seen after the breast cancer surgery include postoperative nausea and vomiting (PONV) or delayed hospital discharge during the acute phase and persistent postsurgical pain or cancer recurrence during the chronic phase [6]. The various analgesic techniques that have been reported to improve the perioperative pain conditions include regional analgesia, opioid analgesia, and perioperative medications. Moreover, there is now accumulating evidence that shows the importance of the analgesic choice in reducing the postoperative comorbidity [7]. The purpose of this study was to review the previous literature and then present the current view of the relationship between the analgesic option and perioperative comorbidity.
2. Quality of Recovery after the Surgery

Adequate recovery of health status early after the surgery is an important clinical endpoint. Traditionally, postsurgical recovery status has been estimated indirectly from several indices including length of hospital stay, length of recovery room stay, or PONV [8]. Recently, an established systemic scoring system, which is referred to as the “quality of recovery-40 (QOR-40)” [9], is now being used to evaluate recovery status has been estimated indirectly from several indices including length of hospital stay, length of recovery room stay, or PONV [8]. Recently, an established systemic scoring system, which is referred to as the “quality of recovery-40 (QOR-40)” [9], is now being used to evaluate recovery status has been estimated indirectly from several indices including length of hospital stay, length of recovery room stay, or PONV [8]. Recently, an established systemic scoring system, which is referred to as the “quality of recovery-40 (QOR-40)” [9], is now being used to evaluate recovery status has been estimated indirectly from several indices including length of hospital stay, length of recovery room stay, or PONV [8]. Recently, an established systemic scoring system, which is referred to as the “quality of recovery-40 (QOR-40)” [9], is now being used to evaluate recovery status has been estimated indirectly from several indices including length of hospital stay, length of recovery room stay, or PONV [8].

2.1. Regional Analgesia. One of the most intensively investigated regional analgesia treatments in the breast cancer surgery is the paravertebral block (PVB) [2]. When combined with general anesthesia, PVB provides superior pain control after breast cancer surgery [10]. Use of a single shot PVB prior to the surgery reduces the recovery time from anesthesia and the incidence of PONV [11]. A retrospective study suggested that PVB could reduce both the length of the hospital stay and the incidence of PONV, provided the patient underwent mastectomy with immediate reconstruction [12]. Another more recently published retrospective study showed that PVB reduced opioid use and increased the fraction of patients with early discharge [13]. Beneficial effect was more prominent in patients who received immediate reconstruction. A recently published prospective study showed that, as compared to inhalational general anesthesia, ultrasound-guided PVB combined with total intravenous anesthesia using propofol resulted in a higher ambulatory surgery QoR-40 score along with a lower pain intensity, incidence of PONV [14]. Another prospective study examined the pectoral nerves (PECS) type 1 and 2 blocks that were recently developed for use as regional analgesia during breast cancer surgery. Study findings showed that the addition of the PECS block to the general anesthesia resulted in superior analgesia, along with a lower incidence of PONV and shorter hospital stays [15].

There are inconsistencies among the previous results with regard to the efficacy of the infiltration of local anesthetics (LAs) in the wound. One study has reported that the infiltration of LAs prior to surgery did not influence the quality of the recovery [16]. Another study reported that LA infiltration after the surgery reduced both the pain intensity and the length of the hospital stay [17].

2.2. Systemic Analgesia. Compared to regional analgesia, fewer studies investigated the effect of systemic analgesic drugs on the recovery condition after breast cancer surgery. Preoperative oral gabapentin [18] or pregabalin [19] has been shown to reduce the pain intensity after breast cancer surgery. However, since these drugs do not reduce the incidence of PONV, this suggests that they have a smaller contribution to the quality of the recovery after the surgery. In contrast, the alpha-2 adrenergic receptor agonists, clonidine and dexmedetomidine, have been reported to have a positive effect on the quality of the recovery after surgery. Intravenous injection of clonidine [20] reduced analgesic consumption and PONV incidence, while intravenous dexmedetomidine [21] reduced both the postsurgical tramadol consumption and PONV incidence and increased the QoR-40 score after the surgery. Perioperative magnesium supplementation is associated with lower postsurgical pain and opioid consumption [22] and increased the QoR-40 after breast cancer surgery [23]. Specific treatments have been designed to reduce nausea and vomiting, reduce acute pain levels, and improve the quality of recovery after surgical procedures. Administration of dexamethasone [24] or betamethasone [25] prior to surgery has been shown to be beneficial by preventing PONV after various surgical procedures. Dexamethasone with higher dose has also been shown to reduce the postsurgical pain intensity and analgesic requirement immediately after a mastectomy [26].

Postsurgical pain should be adequately treated since that is one of physiologic disturbances of the good quality of postsurgical recovery [27]. In breast cancer surgery, regional analgesia including PVB and LA infiltration is associated with higher QoR-40 score and reduced PONV incidence and earlier discharge compared to the opioid-based analgesia. Intravenous alpha-2 adrenergic receptor agonists also increase QoR-40 score after the surgery. Occurrence and severity of PONV are closely related to the quality of the postsurgical analgesia. Both postsurgical antiemetic treatment and adequate pain control are necessary to achieve a better postsurgical recovery after breast cancer surgery.

3. Persistent Postsurgical Pain

Multiple investigations have attempted to identify useful treatment options for the prevention of persistent postsurgical pain after breast cancer surgeries (Table 2). Continuous local treatment with LA, single shot or continuous PVB, intravenous lidocaine, and preoperative selective serotonin-noradrenaline reuptake inhibitor successfully prevent occurrence of persistent pain after the breast cancer surgery.

3.1. Regional Analgesia. Two randomized controlled studies showed that while ropivacaine infiltration into the wound at the end of surgery reduced acute pain intensity, it had no effect either on the pain intensity at 2 months [28] or on the incidence of postsurgical pain between 3 and 12 months [29]. The results of these studies showed that the chronic pain incidence at 3 months after the surgery was 33 and 27% in the ropivacaine and saline group, respectively. In contrast, a repeated treatment using the eutectic mixture of local anesthetics (EMLA) started prior to the surgery and continued daily for 4 days after the surgery and reduced both the incidence and intensity of the pain at 3 months after the surgery [30]. A 50-hour continuous wound infusion of levobupivacaine administered to patients after undergoing breast cancer surgery with immediate tissue expander reconstruction reduced the incidence of persistent postsurgical pain for 3 months after the procedure [31].
Table 1: Analgesic effect on the quality of recovery after the surgery.

| Surgical procedure                                                                 | Analgesic modality                        | Outcomes                                                                 | Study design     | Sample size | Journals (year)           | 1st author | Citation |
|------------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------|-----------------|-------------|--------------------------|------------|----------|
| Nerve block                                                                        |                                            |                                                                          | N = 344         | Ann. Surg. Oncol. (2013) | Coopey [12] |
| Mastectomy plus immediate reconstruction                                          | PVB with Bupivacaine 0.5% versus nonblock | Reduced length of stay and PONV in PVB group                            | Retrospective study |            |                          |            |          |
| Mastectomy with or without immediate reconstruction                                | PVB versus nonblock                       | PVB reduced PONV incidence                                               | Retrospective study | N = 526     | Ann. Surg. Oncol. (2014) | Fahy [13]  |          |
| Pt mastectomy with SLNB, mastectomy with or without SLNB or ALND, and mastectomy with reconstruction | PVB with ropivacaine 0.5% versus sham block | Higher QoR score, reduced discharge time, and reduced PONV in PVB group | Prospective study | N = 66      | Anesthesiology (2014)    | Abdallah [14] |          |
| Mastectomy with ALND                                                               | PECS versus nonblock                      | PECS reduced PONV incidence                                              | Prospective study | N = 120     | Reg. Anesth. Pain Med. (2015) | Bashandy [15] |          |

LA injection at surgical site

| Surgical procedure                                                                 | Analgesic modality                        | Outcomes                                                                 | Study design     | Sample size | Journals (year)           | 1st author | Citation |
|------------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------|-----------------|-------------|--------------------------|------------|----------|
| Pt mastectomy with or without ALND                                                | Ropivacaine 0.375% versus saline before surgery | Incidence of PONV did not change between two groups                      | Prospective study | N = 60      | Acta Anaesthesiol. Scand. (2000) | Johansson [16] |          |
| Mastectomy with ALND                                                              | Bupivacaine 0.25% versus noninjection     | Reduced hospital stay pain intensity in bupivacaine group                | Retrospective study | N = 139     | Acta Chir. Belg. (2011)    | Lu [17]    |          |

Systemic analgesic drug

| Surgical procedure                                                                 | Analgesic modality                        | Outcomes                                                                 | Study design     | Sample size | Journals (year)           | 1st author | Citation |
|------------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------------------------------------------|-----------------|-------------|--------------------------|------------|----------|
| Mastectomy with or without ALND, Pt mastectomy with or without ALND               | Clonidine or placebo                      | Clonidine reduced PONV incidence                                         | Prospective study | N = 68      | Anesthesiology (2002)    | Oddby-Muhrbeck [20] |
| Mastectomy with ALND                                                              | Dexmedetomidine or saline                 | Higher QoR score in dexmedetomidine group                               | Prospective study | N = 92      | Minerva Anesthesiol. (2013) | Kim [21]   |          |
| Mastectomy with ALND                                                              | Gabapentin or placebo before surgery      | Gabapentin reduced pain intensity but not PONV incidence                 | Prospective study | N = 65      | Anesthesiology (2002)    | Dirks [18] |          |
| Mastectomy with or without ALND, Pt mastectomy with or without ALND               | Pregabalin or placebo before surgery      | Pregabalin reduced pain intensity but not PONV incidence                 | Prospective study | N = 84      | Acta Anaesthesiol. Scand. (2011) | Kim [19]   |          |
| Pt mastectomy with or without ALND                                                | Magnesium or saline                       | Higher QoR score in magnesium group Incidence of PONV and intensity of pain reduced in dexamethasone group | Prospective study | N = 46      | Magnes. Res. (2013)       | de Oliveira [22] |
| Mastectomy with ALND                                                              | Dexamethasone or placebo                  | Incidence of PONV and intensity of pain reduced in dexamethasone group | Prospective study | N = 70      | BMC Cancer (2010)         | Gómez-Hernández [26] |
| Pt mastectomy with or without ALND                                                | Betamethasone or no-treatment control     | Incidence of PONV and intensity of pain reduced in betamethasone group  | Prospective study | N = 75      | J. Clin. Anesth. (2014)   | Olanders [25] |          |

Pt mastectomy: partial mastectomy, SLNB: sentinel lymph node biopsy, and ALND: axillary lymph node dissection.
| Surgical procedure                                                                 | Analgesic modality                                                                 | Outcomes                                                                 | Study design     | Sample size | Journals (year)          | Ist author       | Citation                  |
|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------|-------------|--------------------------|------------------|--------------------------|
| Pt mastectomy with or without ALND, mastectomy with or without ALND              | Nerve block PVB with 0.5% bupivacaine versus saline before surgery                  | Intensity and prevalence of pain reduced 12 mo after the surgery         | Prospective study| \(N = 60\)  | Anesth. Analg. (2006)   | Kairaluoma       | [33]                     |
| Pt mastectomy with ALND, mastectomy with or without ALND or SLNB                 | Nerve block PVB with 0.5% ropivacaine before surgery versus wound injection with 0.5% ropivacaine at the end of surgery | Prevalence of pain 12 mo after the surgery was similarly low in both groups | Prospective study| \(N = 129\) | Ann. Surg. Oncol. (2014) | Chiu             | [34]                     |
| Mastectomy with or without ALND                                                  | Nerve block PVB with 0.4% ropivacaine versus saline daily for 3 days after the surgery | Prevalence of pain 12 mo after the surgery was lower in PVB group       | Prospective study| \(N = 60\)  | Ann. Surg. Oncol. (2014) | Ilfeld           | [35]                     |
| Mastectomy with ALND, Pt mastectomy with ALND                                   | LA injection at surgical site EMLA versus placebo for 4 days after the surgery    | Pain at the surgical site reduced 3 mo after the surgery                | Prospective study| \(N = 46\)  | Reg. Anesth. Pain Med. (2000) | Fassoulaki       | [30]                     |
| Mastectomy with ALND, Pt mastectomy with ALND                                   | Ropivacaine 0.75% versus saline at the end of surgery                              | Similar pain condition 2 mo after the surgery                           | Prospective study| \(N = 46\)  | BMC Anesthesiol. (2011)  | Vigneau          | [28]                     |
| Pt mastectomy with ALND, mastectomy with or without ALND or SLNB                 | Ropivacaine 0.375% versus saline at the end of surgery                              | Similar pain condition 3-12 mo after the surgery                        | Prospective study| \(N = 236\)| Anesthesiology (2013)   | Albi-Feldzer      | [29]                     |
| Mastectomy with reconstruction                                                   | Levobupivacaine reduced pain intensity 3 mo after the surgery                      | Levobupivacaine reduced pain intensity 3 mo after the surgery           | Prospective study| \(N = 60\)  | World J. Surg. Oncol. (2014) | Strazisar       | [31]                     |
| Mastectomy with ALND, Pt mastectomy with ALND                                   | Systemic analgesic drug Mexiletine versus gabapentin versus placebo for 10 days    | Intensity and incidence of pain 3 months after the surgery were similar. Sensation of burning pain reduced in mexiletine and gabapentin group | Prospective study| \(N = 67\)  | Anesth. Analg. (2002)   | Fassoulaki        | [38]                     |
| Mastectomy with ALND, Pt mastectomy with ALND                                   | Systemic analgesic drug Venlafaxine versus gabapentin versus placebo for 10 days after the surgery | Venlafaxine reduced the incidence of pain 6 mo after the surgery         | Prospective study| \(N = 150\) | Clin. J. Pain (2010)    | Amr             | [37]                     |
| Pt Mastectomy with ALND or SLNB, mastectomy with ALND or SLNB                   | Systemic analgesic drug IV lidocaine versus saline during the surgery                | Prevalence of pain 3 mo after the surgery reduced in lidocaine group    | Prospective study| \(N = 36\)  | Clin. J. Pain (2012)    | Grigoras         | [36]                     |

Pt mastectomy: partial mastectomy, SLNB: sentinel lymph node biopsy, and ALND: axillary lymph node dissection.
A prospective study that investigated the effect of a single shot PVB at the T3 level prior to surgery found a successful reduction in the acute pain immediately after the surgery [32]. A follow-up study further demonstrated that, as compared to the saline-treated controls, PVB reduced the postsurgical pain for 12 months after the surgery during both resting conditions and when the patient was moving [33]. In another prospective study that compared the effect of PVB and repeated LA wound infiltration on persistent postsurgical pain at 12 months after the surgery, the results indicated that it was not possible to detect any superiority of the PVB versus the LA infiltration [34]. A low persistent postsurgical pain incidence was observed in both groups at 12 months after the surgery (9% for the PVB group versus 7% for the LA group).

A different prospective study investigated the effect of continuous PVB for 3 days after surgery [35]. The experimental group received 5 mL/hour of 0.4% ropivacaine whereas the control group received only saline. Both groups received a single shot PVB with 15 mL of 0.4% ropivacaine prior to the surgery. The continuous ropivacaine infusion in the experimental group reduced the pain intensity and provided better physical and emotional function at 12 months after the surgery.

3.2. Systemic Analgesia. Studies have shown that interventions with systemic analgesic drugs have an effect on the incidence or severity of the persistent postsurgical pain. A prospective randomized study that examined the administration of intravenous lidocaine during breast cancer surgery found that a positive effect on the persistent postsurgical pain was present after the procedure [36]. The patients in this study received a bolus injection of 1.5 mg/kg of either lidocaine or saline, with all patients at the end of the surgery, and then were administered a continuous infusion at 1.5 mg/kg/hour of the same solution initially received. Lidocaine reduced the pain intensity during movement for 4 hours after the surgery and the incidence of persistent postsurgical pain for 3 months after the surgery. A different prospective study investigated the effect of presurgical oral treatments that used either the selective serotonin-noradrenaline reuptake inhibitor (venlafaxine, 37.5 mg) or gabapentin (300 mg) [37]. Although there was a reduction in the acute postsurgical pain intensity in the gabapentin but not the venlafaxine group, there was a reduction in the persistent postsurgical pain incidence in the venlafaxine but not the gabapentin group. A previous study that administered gabapentin (1200 mg/day) or mexiletine (600 mg/day) found that symptoms associated with persistent postsurgical pain except for the burning sensation were similar between both groups and the control group [38].

In a population-based study performed in Norway, 20% of the postsurgical patients reported moderate-to-severe pain in the area of the surgery [39]. In a Canadian retrospective survey that examined patients who did not take any opioids prior to their surgery, 49.2% required an opioid prescription at time of their discharge, with 3% continuing to receive these opioids for 90 days after the surgery [40]. The prevalence of postsurgical pain has been shown to be strongly affected by the type of the surgical procedure, with the prevalence of persistent postsurgical pain highest in thoracic and breast surgery, followed by joint surgery of the knee and hip [41]. The most common factors associated with postmastectomy pain syndrome include a younger age, the type of surgical procedure (lymph node sectioning), and the presence of severe acute pain [42]. Evidences showed that continuous local treatment with LA, single shot or continuous PVB, intravenous lidocaine, and preoperative selective serotonin-noradrenaline reuptake inhibitor successfully prevent occurrence of persistent pain after the breast cancer surgery. It is worth noting that analgesic modalities reduce acute pain and do not always prevent persistent pain after the breast cancer surgery. Future studies on the mechanisms of the chronicity of the surgical pain might be of benefit in helping to determine novel therapeutic approaches that can be used to prevent persistent pain after surgery.

4. Cancer Recurrence

The stress response against the surgery impairs innate and adaptive immune function. Diminished host defense allows progressing postsurgical metastasis or recurrence of the cancer. Regional anesthesia is supposed to preserve postsurgical immune function and may improve cancer recurrence [43]. One study suggested that regional analgesia could prevent the recurrence after the breast cancer surgery [44].

One retrospective study investigated the relationship between the perioperative analgesic modality (regional analgesia with PVB or systemic morphine analgesia) and cancer survival [44]. Recurrence- and metastasis-free survival rates at 24 and 36 months were significantly higher in patients receiving PVB versus systemic morphine. As compared to patients who received sevoflurane-opioid anesthesia after the surgery, those who were administered a combination of propofol-PVB anesthesia showed reduced levels of plasma protumorigenic cytokines that included IL-1 beta, MMP3, and MMP9 [45]. Patients who received propofol-PVB exhibited increased plasma levels of IL-10, which is one of the major antitumorigenic cytokines. In vitro studies that examined patients who received general anesthesia without PVB found that the serum from these patients facilitated the proliferation of a cultured breast cancer cell line [46] and inhibited the antitumor immune activity of the natural killer T cell [47]. In another retrospective study that examined the use of different analgesics during breast cancer surgery, the cancer recurrence rate was lower when patients were treated with ketorolac [48]. The other analgesics including opioids, ketamine, and clonidine did not have any effect on the recurrence rate. The authors of this previous study suggested that the positive effect of ketorolac might be associated with an inhibitory effect on the perioperative production of prostaglandin, which is a known strong inhibitor of anticancer immunity (Table 3).

Neuroendocrine stress responses due to surgical procedures can lead to the inhibition of a patient's immune function. When combined with the inflammatory reaction that occurs after these procedures, it is possible that these surgeries might cause a patient to develop a “protumorigenic” condition [43]. Several studies have demonstrated that the postsurgical analgesic modality modifies both the surgical
stress and inflammatory reaction and additionally influences the cancer recurrence or metastasis after the surgery. Data from these studies have shown that regional analgesia might increase the percentage of recurrence-free/metastasis-free patients after surgeries for gastrointestinal cancer, gynecological cancer, urological cancer, and breast cancer [49]. It should be emphasized, however, that, due to the heterogeneity of the results of these previous clinical studies, no analgesic technique has been definitively proven to increase the survival rate of a particular cancer. More definitive evidence is awaited from an ongoing prospective study investigating the effect of PVB on the cancer recurrence that will be complete in 2019 [50].

5. Conclusion
Not a small number of investigations about acute pain treatment after the breast cancer surgery have reported the effect of analgesic regimen on the occurrence/severity of surgical comorbidity including recovery condition, persistent postsurgical pain, and cancer recurrence. Accumulating evidence has shown that while most of the analgesic modalities can suppress the postsurgical pain intensity, not all of these analgesics can suppress the postsurgical comorbidity. Therefore, analgesic modalities need to be determined based on the feasibility of the modality achieving an effect on the postsurgical comorbidity.

Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

References
[1] American Cancer Society, 2015, http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics.
[2] J. Katz, E. L. Poleshuck, C. H. Andrus et al., “Risk factors for acute pain and its persistence following breast cancer surgery,” Pain, vol. 119, no. 1-3, pp. 16–25, 2005.
[3] M. S. Wallace, A. M. Wallace, J. Lee, and M. K. Dobke, “Pain after breast surgery: a survey of 282 women,” Pain, vol. 66, no. 2-3, pp. 195–205, 1996.
[4] M. Legeby, M. Segerdahl, K. Sandelin, M. Wickman, K. Östman, and C. Olofsson, “Immediate reconstruction in breast cancer surgery requires intensive post-operative pain treatment but the effects of axillary dissection may be more predictive of chronic pain,” Breast, vol. 11, no. 2, pp. 156–162, 2002.
[5] R. H. Baron, J. V. Fey, P. I. Borgen, K. R. Hardick, and K. J. Van Zee, “Eighteen sensations after breast cancer surgery: a 5-year comparison of sentinel lymph node biopsy and axillary lymph node dissection,” Annals of Surgical Oncology, vol. 14, no. 5, pp. 1653–1661, 2007.
[6] A. Prabhakar, K. F. Mancuso, C. P. Owen et al., “Perioperative analgesia outcomes and strategies,” Best Practice and Research: Clinical Anaesthesiology, vol. 28, no. 2, pp. 105–115, 2014.
[7] M. Curatolo, “Adding regional analgesia to general anaesthesia: increase of risk or improved outcome?” European Journal of Anaesthesiology, vol. 27, no. 7, pp. 586–591, 2010.
[8] A. Lee and M. E. Lum, “Measuring anaesthetic outcomes,” Anaesthesia and Intensive Care, vol. 24, no. 6, pp. 685–693, 1996.
[9] P. S. Myles, B. Weitkamp, K. Jones, J. Melick, and S. Hensen, “Validity and reliability of a postoperative quality of recovery score: the QoR-40,” British Journal of Anaesthesia, vol. 84, no. 11, pp. 11–15, 2000.
[10] J. C. Boughey, F. Goravanchi, R. N. Parris et al., “Prospective randomized trial of paravertebral block for patients undergoing breast cancer surgery,” The American Journal of Surgery, vol. 198, no. 5, pp. 720–725, 2009.
[11] F. Pusch, H. Freitag, C. Weinberger, E. Huber, and E. Wildling, “Single-injection paravertebral block compared to general anaesthesia in breast surgery,” Acta Anaesthesiologica Scandinavica, vol. 43, no. 7, pp. 770–774, 1999.
[12] S. B. Coopeny, M. C. Specht, L. Warren, B. L. Smith, J. M. Winograd, and K. Fleischmann, “Use of preoperative paravertebral block decreases length of stay in patients undergoing mastectomy plus immediate reconstruction,” Annals of Surgical Oncology, vol. 20, no. 4, pp. 1282–1286, 2013.
[13] A. S. Fahy, J. W. Jakub, B. M. Dy et al., “Paravertebral blocks in patients undergoing mastectomy with or without immediate reconstruction provides improved pain control and decreased postoperative nausea and vomiting,” Annals of Surgical Oncology, vol. 21, no. 10, pp. 3284–3289, 2014.
[14] F. W. Abdallah, P. J. Morgan, T. Gil et al., “Ultrasound-guided multilevel paravertebral blocks and total intravenous anesthesia improve the quality of recovery after ambulatory breast tumor resection,” Anesthesiology, vol. 120, no. 3, pp. 703–713, 2014.
[15] G. M. Bashandy and D. N. Abbas, “Pectoral nerves I and II blocks in multimodal analgesia for breast cancer surgery:

![Table 3: Analgesic effect on the cancer recurrence.](image)
a randomized clinical trial,” *Regional Anesthesia and Pain Medicine*, vol. 40, no. 1, pp. 68–74, 2015.

[16] A. Johansson, J. Axelsson, C. Ingvart, H.-H. Luttropp, and J. Lundberg, “Preoperative ropivacaine infiltration in breast surgery,” *Acta Anaesthesiologica Scandinavica*, vol. 44, no. 9, pp. 1093–1098, 2000.

[17] T.-J. Lu, J.-H. Chen, H.-M. Hsu, C.-T. Wu, and J.-C. Yu, “Efficiency of infiltration with bupivacain after modified radical mastectomy,” *Acta Chirurgica Belgica*, vol. 111, no. 6, pp. 360–363, 2011.

[18] J. Dirks, B. B. Fredensborg, D. Christensen, J. S. Fomsgaard, H. Flyger, and J. B. Dahl, “A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy,” *Anesthesiology*, vol. 97, no. 3, pp. 560–564, 2002.

[19] S. Y. Kim, J. W. Song, B. Park, S. Park, Y. J. An, and Y. H. Shim, “Pregabalin reduces post-operative pain after mastectomy: a double-blind, randomized, placebo-controlled study,” *Acta Anaesthesiologica Scandinavica*, vol. 55, no. 3, pp. 290–296, 2011.

[20] E. Oddby-Muhrzeck, S. Eksborg, H. T. G. Bergendahl, O. Muhrbeck, and P. A. Lönqvist, “Effects of clonidine on postoperative nausea and vomiting in breast cancer surgery,” *Anesthesiology*, vol. 96, no. 5, pp. 1109–1114, 2002.

[21] S. H. Kim, Y. J. Oh, B. W. Park, J. Sim, and Y. S. Choi, “Effects of single-dose dexmedetomidine on the quality of recovery after modified radical mastectomy: a randomised controlled trial,” *Minerva Anestesiologica*, vol. 79, no. 11, pp. 1248–1258, 2013.

[22] G. S. de Oliveira Jr., L. J. Castro-Alves, J. H. Khan, and R. J. McCarthy, “Perioperative systemic magnesium to minimize postoperative pain meta-analysis of randomized controlled trials,” *Anesthesiology*, vol. 119, no. 1, pp. 178–190, 2013.

[23] G. S. De Oliveira, J. Białek, P. Fitzgerald, J. Y. S. Kim, and R. J. McCarthy, “Systemic magnesium to improve quality of post-surgical recovery in outpatient segmental mastectomy: a randomized, double-blind, placebo-controlled trial,” *Magnetum Research*, vol. 26, no. 4, pp. 156–164, 2014.

[24] G. S. De Oliveira Jr., L. J. S. Castro-Alves, S. Ahmad, M. C. Kendall, and R. J. McCarthy, “Dexamethasone to prevent postoperative nausea and vomiting: an updated meta-analysis of randomized controlled trials,” *Anesthesia & Analgesia*, vol. 116, no. 1, pp. 58–74, 2013.

[25] K. J. Olanders, G. A. E. Lundgren, and A. M. G. Johansson, “Betamethasone in prevention of postoperative nausea and vomiting following breast surgery,” *Journal of Clinical Anesthesia*, vol. 26, no. 6, pp. 461–465, 2014.

[26] J. Gómez-Hernández, A. L. Orozco-Alatorre, M. Domínguez-Contreras et al., “Preoperative dexmedetomidine reduces postoperative pain, nausea and vomiting following breast cancer surgery,” *Clinical Journal of Pain*, vol. 30, no. 7, pp. 589–597, 2014.

[27] R. D. Miller and H. C. Neal, *Miller’s Anesthesia*, Saunders Elsevier, 8th edition, 2015.

[28] A. Vigneau, A. Salengro, J. Berger et al., “A double blind randomized trial of wound infiltration with ropivacaine after breast cancer surgery with axillary nodes dissection,” *BMC Cancer*, vol. 10, article 692, 2010.

[29] A. Albi-Feldzer, E. Mouret-Fourme E, S. Hamouda et al., “A double-blind randomized trial of wound and intercostal space infiltration with ropivacaine during breast cancer surgery: effects on chronic postoperative pain,” *Anesthesiology*, vol. 118, no. 2, pp. 318–326, 2013.

[30] A. Fassoulaki, C. Sarantopoulos, A. Melemeni, and Q. Hogan, “EMLA reduces acute and chronic pain after breast surgery for cancer,” *Regional Anesthesia and Pain Medicine*, vol. 25, no. 4, pp. 350–355, 2000.

[31] B. Strazisar, N. Besic, and U. Ahcan, “Does a continuous local anaesthetic pain treatment after immediate tissue expander reconstruction in breast carcinoma patients more efficiently reduce acute postoperative pain—a prospective randomised study,” *World Journal of Surgical Oncology*, vol. 12, article 16, 2014.

[32] P. M. Kairaluoma, M. S. Bachmann, A. K. Korpinen, P. H. Rosenberg, and P. J. Pere, “Single-injection paravertebral block before general anesthesia enhances analgesia after breast cancer surgery with and without associated lymph node biopsy,” *Anesthesia and Analgesia*, vol. 99, no. 6, pp. 1837–1843, 2004.

[33] P. M. Kairaluoma, M. S. Bachmann, P. H. Rosenberg, and P. J. Pere, “Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery,” *Anesthesia & Analgesia*, vol. 103, no. 3, pp. 703–708, 2006.

[34] M. Chiu, G. L. Bryson, A. Lui, J. M. Watters, M. Taljaard, and H. J. Nathan, “Reducing persistent postoperative pain and disability 1 year after breast cancer surgery: a randomized, controlled trial comparing thoracic paravertebral block to local anesthetic infiltration,” *Annals of Surgical Oncology*, vol. 21, no. 3, pp. 795–801, 2014.

[35] B. M. Ilfeld, S. J. Madison, P. J. Suresh et al., “Persistent postmastectomy pain and pain-related physical and emotional functioning with and without a continuous paravertebral nerve block: a prospective 1-year follow-up assessment of a randomized, triple-masked, placebo-controlled study,” *Annals of Surgical Oncology*, vol. 22, no. 6, pp. 2017–2025, 2014.

[36] A. Grigoras, P. Lee, F. Sattar, and G. Shorten, “Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery,” *Clinical Journal of Pain*, vol. 28, no. 7, pp. 567–572, 2012.

[37] Y. M. Amr and A. A. A.-M. Yousef, “Evaluation of efficacy of the perioperative administration of Venlafaxine or gabapentin on acute and chronic postmastectomy pain,” *The Clinical Journal of Pain*, vol. 26, no. 5, pp. 381–385, 2010.

[38] A. Fassoulaki, K. Patris, C. Sarantopoulos, and Q. Hogan, “The analgesic effect of gabapentin and mexiletine after breast surgery for cancer,” *Anesthesia & Analgesia*, vol. 95, no. 4, pp. 985–991, 2002.

[39] A. Johansen, L. Romundstad, C. S. Nielsen, H. Schirmer, and A. Stubbhaug, “Persistent postsurgical pain in a general population: prevalence and predictors in the Tromsø study,” *Pain*, vol. 153, no. 7, pp. 1390–1396, 2012.

[40] H. Clarke, N. Soneji, D. T. Ko, L. Yun, and D. N. Wijesundera, “Rates and risk factors for prolonged opioid use after major surgery: population based cohort study,” *British Medical Journal*, vol. 348, Article ID g1251, 2014.

[41] S. Haroutiunian, L. Nikolajsen, N. B. Finnerup, and T. S. Jensen, “The neuropathic component in persistent postsurgical pain: a systematic literature review,” *Pain*, vol. 154, no. 1, pp. 95–102, 2013.

[42] K. G. Andersen and H. Kehlet, “Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention,” *Journal of Pain*, vol. 12, no. 7, pp. 725–746, 2011.

[43] J. P. Cata, V. Gottumukkala, and D. L. Sessler, “How regional analgesia might reduce postoperative cancer recurrence,” *European Journal of Pain Supplements*, vol. 5, no. 2, pp. 345–355, 2011.

[44] A. K. Exadaktylos, D. J. Buggy, D. C. Moriarty, E. Mascha, and D. I. Sessler, “Can anesthetic technique for primary breast cancer
surgery affect recurrence or metastasis?” Anesthesiology, vol. 105, no. 4, pp. 660–664, 2006.

[45] C. A. Deegan, D. Murray, P. Doran et al., “Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery,” Regional Anesthesia & Pain Medicine, vol. 35, no. 6, pp. 490–495, 2010.

[46] C. A. Deegan, D. Murray, P. Doran, P. Ecimovic, D. C. Moriarty, and D. J. Buggy, “Effect of anaesthetic technique on oestrogen receptor-negative breast cancer cell function in vitro,” British Journal of Anaesthesia, vol. 103, no. 5, pp. 685–690, 2009.

[47] A. Buckley, S. McQuaid, P. Johnson, and D. J. Buggy, “Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: a pilot study,” British Journal of Anaesthesia, vol. 113, supplement 1, pp. i56–i62, 2014.

[48] P. Forget, J. Vandenhende, M. Berliere et al., “Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis,” Anesthesia and Analgesia, vol. 110, no. 6, pp. 1630–1635, 2010.

[49] J. P. Cata, M. Hernandez, V. O. Lewis, and A. Kurz, “Can regional anesthesia and analgesia prolong cancer survival after orthopaedic oncologic surgery?” Clinical Orthopaedics and Related Research, vol. 472, no. 5, pp. 1434–1441, 2014.

[50] J. Wu, D. Buggy, E. Fleischmann et al., “Thoracic paravertebral regional anesthesia improves analgesia after breast cancer surgery: a randomized controlled multicentre clinical trial,” Canadian Journal of Anesthesia, vol. 62, no. 3, pp. 241–251, 2015.