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Review Article

An Evidence-Based Review of the Efficacy of Perioperative Analgesic Techniques for Breast Cancer-Related Surgery

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Abstract

Objective. To review the published evidence regarding perioperative analgesic techniques for breast cancer–related surgery.

Design. Topical review.

Methods. Randomized, controlled trials (RCTs) were selected for inclusion in the review. Also included were large prospective series providing estimates of potential risks and technical reports and small case series demonstrating a new technique or approaches of interest to clinicians.

Results. A total of 514 abstracts were reviewed, with 284 studies meeting criteria for full review. The evidence regarding preemptive ketamine, scheduled opioids, perioperative non-steroidal anti-inflammatory drugs (NSAIDs), and intravenous lidocaine is mixed and deserves further investigation. There is strong evidence that both pregabalin and gabapentin provide analgesic benefits following breast surgery. There is minimal and conflicting data from high-quality randomized, controlled studies suggesting that directly infiltrating and/or infusing local anesthetic (liposome encapsulated or unencapsulated) into the surgical wound is a reliably effective analgesic. In contrast, there is a plethora of data demonstrating the potent analgesia, opioid sparing, and decreased opioid-related side effects from thoracic epidural infusion and both single-injection and continuous paravertebral nerve blocks (the latter two demonstrating decreased persistent post-surgical pain between 2.5 and 12 months). Techniques with limited—yet promising—data deserving additional investigation include brachial plexus blocks, cervical epidural infusion, interfascial plane blocks, and interpleural blocks.

Conclusions. While there are currently multiple promising analgesic techniques for surgical procedures of the breast that deserve further study, the only modalities demonstrated to provide potent, consistent perioperative pain control are thoracic epidural infusion and paravertebral nerve blocks.

Key Words. Mastectomy; Breast Surgery; Analgesia; Pain Control; Persistent Post-Surgical Pain; Chronic Postoperative Pain

Introduction

With the exception of skin cancer [1], breast cancer is the most common cancer in women with over 230,000 new cases diagnosed annually within the United States alone [2]. Surgery is the mainstay of treatment [3], with

40% of women experiencing acute postoperative pain and 25–60% developing persistent postsurgical pain [4–8]. Pain control is usually provided with a combination of oral and intravenous analgesics, in addition to local and regional techniques such as local anesthetic infiltration [9,10], intercostal block [11], paravertebral block [12–16], and thoracic epidural anesthesia [17]. This article is a systematic review of the published literature involving post–breast surgery analgesic techniques.

Methods

The authors searched the US National Library of Medicine's public Medline database. Criteria included the time period from 1966 through August 2015, as well as the terms "breast surgery," "breast cancer surgery," "mastectomy," and "analgesia." Initially, a total of 484 articles were identified, and the abstracts of each reviewed for content. Criteria for further inclusion in the review encompassed randomized, controlled trials (RCTs), although in some cases technical reports and small series of subjects demonstrating a new technique or approaches were retained, as well as large prospective series providing estimates of potential risks. The reference lists of the remaining 254 articles were further reviewed for additional publications that met inclusion criteria.

Results

A total of 514 abstracts were reviewed, with 284 studies meeting criteria for full review. A conspicuous lack of data from randomized, placebo-controlled trials involving oral and intravenous analgesics was noted.

Pharmacologic

Ketamine

Ketamine is an N-methyl-D-aspartate receptor inhibitor and commonly used to provide perioperative analgesia. Unfortunately, there is limited data involving the use of ketamine for procedures of the breast. In an RCT evaluating for this effect, patients undergoing mastectomy were randomized to receive a single dose of ketamine (0.15 mg/kg IV) either before surgery or at the time of skin closure [18]. While patients who received ketamine at the end of surgery used less morphine within the first 2 postoperative hours, no other differences in pain scores or opioid use were seen throughout the 24-hour postoperative study period between the groups. As no decrease in pain scores or morphine consumption was seen in the group who received ketamine before surgery, no evidence of a preemptive analgesic effect was found. Considering the plethora of evidence that ketamine provides perioperative analgesia for multiple procedures other than breast surgery, it is probable that ketamine is beneficial for breast surgery—however, a dearth of evidence specific to breast surgery precludes any recommendations.

Scheduled Opioids

Opioids are usually titrated to pain level following surgery. However, two RCTs examined scheduled administration—dosing regardless of pain level—on subsequent pain scores and additional opioid requirements [19,20]. In the first of these studies, subjects were randomized to receive either oral controlled-release oxycodone (20 mg) or a placebo 1 hour before mastectomy followed by a second dose 12 hours after the first dose was given. Unsurprisingly, those with active medication reported lower pain scores and required less supplemental opioids within the first 24 postoperative hours; and, no difference in opioid-related side effects were detected. In contrast, an RCT in which randomized subjects received either sustained-release tramadol (100 mg) or placebo administered 1 hour prior to surgery with a second dose 12 hours later detected little difference in postoperative pain scores or opioid consumption [20]. Furthermore, the treatment group experienced more nausea and vomiting. Thus, the evidence for scheduled dosing with opioids is mixed, and deserves further investigation.

Anticonvulsants

Pregabalin and gabapentin, originally developed as antiepileptic drugs, have been used to treat neuropathic pain [21,22]. They effectively decrease postoperative opioid consumption and pain scores for various surgical procedures, including hysterectomy [23,24], spinal surgery [25], and nephrectomy [26]. In breast surgeries, the outcomes are similar. For example, in one RCT a single dose of gabapentin (1200 mg) administered 1 hour prior to surgery resulted in a substantial decrease in postoperative morphine (29 mg vs. 15 mg, $P < 0.0001$) use as well as decreased pain with movement up to 4 hours postoperatively (31 mm vs. 9 mm, $P = 0.018$) [27]. In contrast, no difference in either pain at rest or undesirable side effects was detected. Similarly, pregabalin (75 mg) administered twice daily for seven days decreased postoperative opioid requirement by 70% in patients following augmentation mammoplasty [28]. In a subsequent RCT, subjects who underwent mastectomy were randomized to receive either two doses of pregabalin or placebo 1 hour before surgery and 12 hours after the initial dose [29]. Subjects receiving active medication reported less pain at rest at 1, 24, and 48 hours postoperatively. Lastly, a single 600 mg dose of gabapentin provided 1 hour preoperatively significantly decreased morphine consumption (5.8 mg vs. 11.0 mg, $P < 0.001$) and increased time to first postoperative analgesic dose (90 min vs. 0 min, $P < 0.001$) compared with placebo [30]. In addition, the gabapentin decreased pain at rest and with movement for most time periods up to 12 hours after surgery, with no significant side effects. Thus, there is strong evidence that both pregabalin and gabapentin provide analgesic benefits following breast surgery.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs have been studied extensively when used for multiple surgical procedures excluding the breast—but, surprising, there are few RCTs concerning specifically breast surgery. One investigation randomized subjects having mastectomy to either rectal diclofenac (50 mg) or placebo every 8 hours for three doses [31]. Patients receiving the NSAID experienced less pain at rest during the first 20 hours after surgery (non-significant with motion for the three time periods studied, ranging from 0 to 64 hours postoperatively) and required 30% less opioid rescue analgesics during the first 6 postoperative hours. Though postoperative bleeding was also higher in patients receiving diclofenac, and two patients in this group required blood transfusion, none of the patients needed re-operation for bleeding or hematoma. Based on these findings and those of other studies involving non-breast procedures, though the use of NSAIDs in multimodal analgesic regimens appears to be beneficial, with the risk of possibly increased postoperative bleeding, further research specific to breast surgery is required for conclusive recommendations.

Intravenous Lidocaine

While intravenous lidocaine has demonstrated analgesic benefits in abdominal and thoracic surgeries [32–36] and neuropathic pain states [37], benefits in the perioperative period are lacking when used for breast surgery [38,39]. One study that randomized subjects undergoing mastectomy to either intravenous lidocaine (3 mg/kg) or placebo infused intraoperatively over 1 hour following incision, found no statistically significant differences between the two groups for pain scores or opioid requirements within the first 24 hours [40]. Likewise, when patients undergoing various breast surgeries were randomized to receive either an intravenous lidocaine infusion (1.5 mg/kg/h) or placebo, no significant difference was noted in postoperative pain, analgesic use, hospital length of stay, or patient satisfaction with pain control [41]. The reason for contrasting results between breast and other types of surgery remains unknown.

Interventional

Wound Infiltration

Directly infiltrating local anesthetic into the surgical wound is one of the least technical regional analgesic modalities and concurrently avoids risks of other techniques such as pneumothorax, pleural puncture, and high-volume intravascular injection. Unfortunately, there is minimal data from high-quality RCTs suggesting that it is a reliably effective analgesic [42]. Fifteen RCTs failed to find a statistically significant analgesic benefit [9,10,43–55], while six others found a minimal decrease in pain scores that reached statistical significance for but only a few postoperative hours (Table 1) [50–55]. Importantly, a meta-analysis combining 13 of the trials with a total of 1,150 subjects found only a small incremental improvement in pain scores [weighted mean difference −0.19 (95% CI: −0.39 – 0.00)] at 2 hours postoperatively, with no subsequent benefit detected [56].

Wound infiltration has not been shown to significantly impact opioid use nor the side effects related to them. For example, in one relatively small RCT (n = 79) comparing wound infiltration with 0.25% bupivacaine to placebo in patients undergoing multiple types of breast procedures, the primary end point—pain scores—were low in both groups, with no difference detected between the two. However, the bupivacaine group used 2.9 mg less opioid within the first 24 postoperative hours (bupivacaine 3.4 mg vs. control 7.3 mg, $P = 0.02$) [44]. Unfortunately, with over 15 statistical comparisons, the risk of an erroneous false positive (Type 1 error) is unacceptably high. Regardless, opioid use is a surrogate end point and 2.9 mg decrease of IV morphine equivalents over the course of 24 hours is of dubious benefit—rather, it is the undesired opioid-induced side effects that are important end points. To date, no RCT has demonstrated a reduction in any non-surrogate end points. In other words, there is little existing data demonstrating local anesthetic wound infiltration improving patients' postoperative experience.

Similarly, the use of wound infiltration as a preemptive analgesic to minimize postoperative pain after mastectomy has not been shown to provide benefit. In one RCT, wound infiltration with local anesthetic prior to incision in patients undergoing ambulatory breast surgery offered no advantage when compared to post-incision local anesthetic infiltration [57]. A subsequent RCT incorporated a placebo group into the study design [50], in order to better evaluate any preemptive analgesic effect [58]. Though local anesthetic infiltrated in the area of the incision decreased pain frequency and opioid use until discharge from the recovery room compared to placebo, the timing of its delivery (whether pre-incisional, post-incisional or both) made little difference. Significantly, though the placebo group consumed more supplemental opioid until discharge from the recovery room, there was no increase in postoperative nausea, vomiting, and/or anti-emetic administration [50]. The conclusion is that pre-incisional wound infiltration does not confer a preemptive analgesic effect.

Wound Infusion

A surgically placed catheter inserted directly into the wound allows a continuous infusion or repeated boluses of local anesthetic following surgery. In one positive RCT involving subjects undergoing radical mastectomy [59], all subjects received levobupivacaine 0.25% (30 mL) infiltrated directly into the wound as well as a percutaneous wound catheter at the end of surgery. Individuals were subsequently randomized to receive an infusion of either additional levobupivacaine (0.5%) or

Table 1 Wound infiltration

First Author (Year)	Surgical Procedure	Design	Intervention	Treatment Effect
Albi-Feldzer 2013 [53]	Conservative surgery with ALND, MRM, with or without ALND	Randomized, double-masked	Ropiv 0.375% 3mg/kg mixed with saline (n = 117/236)	Significantly reduced pain at 0–90 min postoperatively, and NS difference in analgesic requirement 0–48 h postoperatively
Baudry 2008 [43]	MRM or partial mastectomy with ALND	Randomized, double-masked	Ropiv 0.475%, 40 ml (n = 40/78)	NS difference, 0–24 h
Campbell 2014 [44]	Mastectomy, WLE, or lumpectomy with or without ALND	Randomized, single-masked	Bupiv 0.25%, 20 ml (n = 4590)	NS, 0–48h, 1 week postoperatively, though less opioid use in first 48 h
Johansson 2003 [10]	Partial mastectomy with or without ALND	Randomized, single-masked	1) Ropiv 0.375%, 0.3 ml/kg (n = 15/45) 2)Ropiv 0.375%, 0.3 ml/kg + fentanyl 0.5 g/kg (n = 15/45)	NS, 0–18 h postoperatively
Johansson 2000 [9]	Partial mastectomy with or without ALND	Randomized, double-masked	Ropiv 0.375% (n = 30/59)	NS, 0–24 h postoperatively
Jonnavithula 2015 [45]	MRM	Randomized, double-masked	Bupiv 0.25%, 20 ml breast, 20 ml axillary drain (n = 20)	Significantly reduced analgesic requirement up to 24h postoperatively
Mohamed 2013 [46]	MRM with ALND	Randomized, double-masked	1) Bupiv 0.5% 5 ml + clonidine 250 micrograms diluted with NS to 15 ml(n = 35) 2) Bupiv 0.5% 5 ml + clonidine 150 micrograms diluted with NS to 15 ml (n = 35) 3) Bupiv 0.5% 5 ml diluted with NS to 15 ml	Significantly reduced analgesic requirement up to 48 h postoperatively, no difference noted amount treatment groups
Pettersson 2001 [47]	Mastectomy with ALND	Randomized, double-masked	1) Bupiv 0.5% 20 ml (n = 29) 2) topical application of lidocaine/prilocaine mixture 10 gm (n = 31)	NS, 0–20 h postoperatively
Rica 2007 [48]	Mastectomy and ALND	Randomized, double-masked	1) Ropiv 0.2% ml diluted to 80 ml, infiltrated preoperatively (n = 15) 2) Ropiv 0.2% ml diluted to 80 ml, infiltrated postoperatively (n = 15)	NS difference in pain severity
Talbot 2004 [49]	MRM	Randomized, double-masked	Bupiv 0.5% 20 ml into axillary drain and q 4hr x 6 doses (n = 19)	NS difference, 0–28 h postoperatively
Vallejo 2006 [50]	Segmental mastectomy without ALND	Randomized, double-masked	1) Bupiv 0.5% 10 ml, pre and post incision wound infiltration (n = 30) 2) Bupiv 0.5% 10 ml, pre incision (n = 30) 3) Bupiv 0.5% 10 ml, postoperative (n = 30)	Significantly reduced pain scores and analgesic requirement in early postoperative period, then no difference
Vigneau 2011 [51]			Ropiv 0.75%, 20 ml (n = 24)	

(continued)

Table 1 Continued

First Author (Year)	Surgical Procedure	Design	Intervention	Treatment Effect
	Mastectomy or lumpectomy with ALND	Randomized, double-masked		Significantly reduced pain at 2, 4, and 6 h postoperatively, and significantly reduced analgesic requirement at 2, 4, 6 h postoperatively
Zielinski 2011 [52]	MRM	Randomized, double-masked	Bupiv 100 mg diluted with NS to 40 ml (n = 57)	Significantly reduced pain score at 4 and 12 h postoperatively and significantly reduced analgesic requirement 4–12 h postoperatively
Rosaeg 1998 [54]	Mammoplasty	Randomized, double-masked	Lidocaine 0.35% with 1:1,000,000 epinephrine, 10 ml/kg, preincisional (n = 15)	Significantly reduced pain score 0–2 h postoperatively and significantly decreased analgesic requirements 0–4.5 h postoperatively
Owen 1985 [55]	Lumpectomy	Randomized, double-masked	Bupiv 0.5%, 10 ml, postoperatively (n = 19)	Significantly reduced pain score 24 h postoperatively, and significantly decreased analgesic requirement for 24 h postoperatively
Ferreira 2014 [59]	MRM	Randomized, double-masked	Levobupivacaine 0.25% 30 ml, followed by 0.5% 2ml/hour infusion x48 h (n = 34) vs infusion with saline (n = 39)	Decreased pain and analgesia use up to 24 h postoperatively, with no difference in rate of nausea/vomiting

ALND = axillary lymph node dissection; MRM = modified radical mastectomy; WLE = wide local excision;ropi = ropivacaine; bupiv = bupivacaine; NS = not significant.

saline (2 mL/h) for 48 hours. The authors reported overwhelming benefits of the levobupivacaine infusion, with subjects reporting dramatically decreased pain scores (overall $P < 0.001$) in the recovery unit (VAS of 2 vs. 7), at 24 h (1 vs 4), and at 48 h (0 vs 3). In addition, the active treatment group consumed less paracetamol, metamizole, and opioids ($P < 0.001$ for all). Remaining unexplained is why—if both treatment groups received levobupivacaine 0.25% (30 mL) infiltrated at the end of surgery—did the group with the placebo infusion demonstrate such a dramatic difference in pain and analgesic requirements within the recovery room? This irregularity calls into question the remainder of the study results, especially since a meta-analysis of four similar RCTs failed to detect a statistically significant difference between a local anesthetic and placebo infusion in any variable at any time point following breast surgery [60].

Liposome Bupivacaine

Bupivacaine HCl is a long-acting local anesthetic commonly used for wound infiltration following breast surgery [61–63]. Any efficacy, however, is limited by its duration of action of approximately 12 hours [64–66]. The development of a depot formulation of bupivacaine attempts to address this issue, as a liposomal formulation allows for the slow release of the local anesthetic over a period measured in days and not hours [67–69]. Although non-randomized, retrospective, unmasked studies have reported dramatic benefits of using liposome bupivacaine infiltration versus both a bupivacaine infusion or no local anesthetic involvement—such as decreasing hospitalization duration and pain scores 40–50% up to 24 hours postoperatively [70]—two randomized, bupivacaine HCl-controlled trials failed to detect any benefits apart from decreased opioid consumption through 48–60 hours [71,72]. Considering the lack of RCT-demonstrated benefits of liposome bupivacaine versus bupivacaine HCl combined with the 100-fold increase in cost of the former over the latter, it appears that additional data demonstrating analgesic or other benefits is warranted prior to widespread adoption of the new formulation. It is notable—and should give pause to practitioners considering replacing bupivacaine HCl with liposome bupivacaine—that of 12 RCTs comparing these two bupivacaine formulations for various procedures including breast surgery, only one involving hemorrhoidectomy demonstrated an analgesic improvement [72–78].

Regional Analgesia

Paravertebral Nerve Blocks: Anatomy and Technique

A thoracic paravertebral block is a regional anesthetic technique in which local anesthetic is injected into a potential space immediately adjacent to a thoracic spinal nerve as it emerges from the intervertebral foramen [79], providing ipsilateral analgesia of the chest and abdomen. This wedge-shaped space lies on either side of the vertebral column [80] and is bounded anterolaterally by the parietal pleura, posteriorly by the superior costotransverse ligament, medially by the vertebrae and intervertebral foramina, and superiorly and inferiorly by the heads of the ribs [81]. Initially detailed in 1905 for abdominal muscle relaxation during surgery, the block was most popular in the first few decades of the twentieth century, before falling out of common practice until the last decades of the same century, with an increasing popularity continuing into the present [79]. Both unilateral and bilateral thoracic paravertebral blocks are used to provide analgesia and anesthesia for breast surgery and may be performed at one or more vertebral levels [82]. Injecting at multiple thoracic levels increases the number of affected dermatomes and improves analgesia duration/quality, but subjects the patient to a higher risk of complications [13,83–85]. In contrast, a single injection improves patients' comfort and requires less sedation to be administered during the block, resulting in higher patient satisfaction [16,86], but carries the theoretical increased risk of bilateral neuraxial spread. In summation, single or multiple injection paravertebral blocks are acceptable, and vigilance with every injection is critical to minimize the complication rate. Described first as a landmark-based technique, electrostimulation and pressure-measurement have since been utilized as tools to assist with block placement [87–89]. In 2009, the use of ultrasound for paravertebral block placement began to appear in the medical literature [90–92]. Since then, a variety of ultrasound-based approaches (and their modifications) has been described [93–96]. Evidence-based recommendations for one technique over another are lacking; preference may depend on personal factors such as ultrasound experience and familiarity with the technique [97].

Paravertebral Blocks: Benefits

Unlike local anesthetic wound infiltration, there is a plethora of data demonstrating the potent analgesia—in addition to opioid sparing—conveyed with paravertebral blocks (Table 2). Using either single-injection or continuous paravertebral nerve blocks [1], investigators have demonstrated statistically significant reductions in pain scores at rest and with movement not only at 2 hours following surgery [1,13–16,85,86,98–107], but at 24 hours [1,13–15,98,99,101–105,107–112], 48 hours [1,13,14,98,103,105,111] and even 72 hours postoperatively [1,13,14,103,105,111]. Three independent meta-analyses provide an estimate of paravertebral block potency and are in agreement, finding a reduction in both average and worst pain scores of approximately 1.7–2.5 points on a 0–10 scale when compared with opioid-based analgesics alone [106,113,114].

The improved analgesia provided with paravertebral blocks results in multiple related benefits, including decreased opioid requirements, opioid-related side effects, and patient satisfaction. Opioid sparing is clearly demonstrated in four independent meta-analyses [106,

Table 2 Paravertebral blocks (PVBs)

First Author (Year)	PVB Type	Study Design	Intervention (n=# with intervention/# total)	Control or Comparison	Treatment Effect
Pusch 1999 [15]	Single injection	RCT	Bupiv 0.5% (n = 44/86)	GA with TIVA	Decreased pain scores
Klein 2000 [13]	Multiple injections	RCT, single-masked	Bupiv 0.5%, epinephrine (n = 29/59)	Propofol sedation	Decreased pain up to 24 h postoperatively
Terheggen 2002 [85]	Single injection	RCT	Bupiv 0.5%, epinephrine (n = 15/30)	Propofol sedation	Decreased pain up to 90 minutes postoperatively
Naja 2003 [111]	Multiple injections	RCT	Lidocaine 1%, bupiv 0.5%, fentanyl, clonidine, epinephrine (n = 30/60)	Propofol sedation	
Buggy 2004 [101]	Continuous infusion	RCT	Levobupivacaine 0.25% (n = 10/20)	GA with isoflurane and nitrous oxide	Decreased pain scores
Kairaluoma 2004 [16]	Single injection	RCT, double-masked	Bupiv 0.5% (n = 30/59)	GA with sevoflurane	Decreased opioid consumption
Paleczny 2005 [117]	Single injection	RCT	Ropiv 0.5%, fentanyl, clonidine (n = 25/49)	GA with propofol and nitrous oxide	Decreased pain scores
Burlacu 2006 [128]	Continuous infusion	RCT, double-masked	Levobupivacaine 0.25%, fentanyl, clonidine (n = 38/52)	GA with sevoflurane and nitrous oxide	Decreased opioid use with fentanyl and clonidine, but increased nausea and hypotension, respectively
Iohom 2006 [103]	Continuous infusion	RCT	Bupiv 0.25% (n = 14/29)	GA with sevoflurane and nitrous oxide	Decreased pain on movement
Kairaluoma 2006 [110]	Single injection	RCT, double-masked	Bupiv 0.5% (n = 30/60)	GA with sevoflurane	No difference in opioid consumption for first 14 days postoperatively
Shkol'nik 2006 [105]	Single injection	RCT	Bupiv 0.125%, ropiv 0.2% (n = 90/180)	GA with TIVA	Decreased pain scores
Dabbagh 2007 [86]	Single injection	RCT	Lidocaine 2% (n = 30/60)	GA with halothane and nitrous oxide	Decreased pain scores up to 6 h postoperatively
Moller 2007 [84]	Multiple injections	RCT, double-masked	Ropiv 0.5% (n = 38/79)	GA with TIVA	Decreased severity or pain and fentanyl use, through PACU stay, no difference after discharge from PACU
Sidiropoulou 2008 [133]	Single injection	RCT	Ropiv 0.5% (n = 24/48)	GA with continuous wound infiltration	Similar opioid consumption and low pain scores; PVB group with lower pain scores 4 h postoperatively; continuous wound infiltration group with lower pain scores 16 and 24 hpostoperatively
Boughey 2009 [109]	Multiple injections	RCT	Ropiv 0.5–1%, epinephrine (n = 39/80)	GA	Decreased pain up to 3 h postoperatively

(continued)

Table 2 Continued

First Author (Year)	PVB Type	Study Design	Intervention (n=# with intervention/# total)	Control or Comparison	Treatment Effect
Arunakul 2010 [99]	Single injection	RCT	Bupiv 0.5% 3ml/kg (n = 10/20)	GA with isoflurane and nitrous oxide	Decreased pain scores at 1 and 24 h, postoperatively
Buckenmaier 2010 [122]	Single injection	RCT, double-masked	1) Ropiv 0.1% (n = 26/73) 2) Ropiv 0.2% (n = 26/73)	GA	No difference in pain scores
Abdel-halim 2011 [107]	Single injection	RCT, single-masked	Lido 2% with epi bolus, then infusion at 5ml/hour (n = 20/40)	GA with isoflurane	Decreased pain up to 8 h postoperatively
Li 2011 [104]	Multiple injections	RCT	Bupiv 0.5% with epi, 3–5 ml at each level (n = 15/40)	GA with desflurane	Decreased pain until midmorning of postoperative day 1
Ibarra 2011 [202]	Single injection	RCT	Ropiv (n = 15)	GA	Lower prevalence of chronic pain at 4–5 months postoperatively
Bhuvaneswari 2012 [108]	Single injection	RCT, double-masked	1) Bupiv 0.25% with epi (n = 12/48) 2) Bupiv 0.25% with epi & fentanyl (n = 12/48) 3) Bupiv 0.5% with epi (n = 12/48)	GA	Decreased analgesic use and pain scores in groups 2 and 3
Das 2012 [102]	Multiple injections	RCT, double-masked	Bupiv 0.5%, 5ml at each level (n = 30/60)	GA volatile with nitrous oxide	Decreased pain scores up to 4 h postoperatively, increased time to first postoperative analgesic
Abdallah 2014 [98]	Multiple injections	RCT, double-masked	Ropiv 0.5%, 25 ml total (n = 33/64)	GA with sevoflurane and nitrous oxide	Decreased pain scores and improved quality of recovery scores until postoperative day 2
Ilfeld 2014 [131]	Continuous infusion	RCT, triple-masked	Ropiv 0.5% with epi (n = 30/60)	GA	Decreased pain on postoperative day 1
Karmakar 2014 [14]	Continuous infusion or single injection	RCT, double-masked	1) Ropiv 2mg/kg with epi then infusion with 0.9% saline (n = 60) 2) Ropiv 2 mg/kg with epi, then infusion with 0.25% ropiv at 0.1 mL/kg/hr (n = 57)	GA with TIVA	No difference in pain or opioid use
Wu 2015 [106]	Continuous infusion or multiple injections	RCT, double-masked	Bupi 0.5% or ropiv 0.5, with epi. CPVB: 6–10 mL/h of either solution up to 48 hr MPVB: ropiv 0.75%, 5 ml at each level (n = 187/386)	GA with sevoflurane	Decreased pain and analgesic consumption

RCT = randomized, controlled trial; bupiv = bupivacaine; ropiv = ropivacaine; epi = epinephrine; GA = general anesthesia; PACU = post-anesthesia care unit; TIVA = total intravenous anesthesia; CPVB = continuous paravertebral block; MPVB = multiple-level paravertebral block.

Table 3 Chronic pain

First Author (Year)	Analgesia Technique	Study Design	Intervention (n=# with intervention/# total)	Control or Comparison	Treatment Effect
Kairaluoma 2006 [110]	Preincision single injection	RCT, single-masked	0.5% bupiv, 1.5 mg/kg at T3 (n = 30/60)	GA (n = 30)	Decreased prevalence of chronic pain 1 year after surgery
Ilfeld 2014 [112]	Continuous infusion	RCT, triple-masked	Ropiv 0.4% infusion for 3 days after single PVB (n = 30/60)	GA with single PVB (n = 30)	Decreased chronic pain at 1 year
Albi-Feldzer 2013 [53]	Wound infiltration	RCT, double-masked	Ropiv 0.375%, 3 mg/kg (n = 117/236)	GA (n = 119)	No decrease in chronic pain
Chiu 2014 [201]	Multiple injections	RCT	Ropiv 0.5% with epi (n = 65/129)	Eound infiltration with ropiv 0.5% with epi	Low incidence of chronic pain at 1 year
Fassoulaki 2005 [197]	Multimodal	RCT, triple-masked	Gabapentin, EMLA, wound infiltration with ropiv 0.75% (n = 49/97)	GA	Decreased chronic pain at 3 months, no difference at 6 months
Iohom 2006 [103]	Continuous infusion	RCT	Bupiv 0.25% (n = 14/29)	GA with sevoflurane and nitrous oxide	Decreased chronic pain at 3 months
Ibarra 2011 [202]	Single injection	RCT	Ropiv (n = 15)	GA	Lower prevalence of chronic pain at 4–5 months postoperatively
Karmakar 2014 [14]	Single injection and continuous infusion	RCT, double-masked	1) Ropiv 2mg/kg with epi then infusion with 0.9% saline (n = 60/177) 2) Ropiv 2 mg/kg with epi, then infusion with 0.25% ropiv at 0.1 mL/kg/h (n = 57/177)	GA with TIVA	No difference in incidence of chronic pain at 3 and 6 months
Fassoulaki 2002 [194]	EMLA	RCT, double-masked	EMLA to sternal, supraclavicular, and axilla (n = 23/45)	GA with sevoflurane and nitrous oxide	Decreased chronic pain at 3 months

RCT = randomized, controlled trial; bupiv = bupivacaine; ropiv = ropivacaine; epi = epinephrine; GA = general anesthesia; PVB = paravertebral block; TIVA = total intravenous anesthesia; EMLA = eutectic mixture of local anesthetics.

113,114], although the degree of opioid sparing varies widely among clinical trials, most likely due to variations in subject populations, surgical procedures, treatment techniques, and multimodal supplemental analgesics. Unsurprisingly, multiple RCTs document decreased postoperative nausea and vomiting with the addition of paravertebral blocks [1,12,15,16,84,85,98,102,104,106–108,111,114–117]. However, there is wide variation regarding the degree of risk reduction—with a few failing to find a statistically significant difference among treatments [100]—again most likely due to variations in multiple population, surgical, intervention, and study factors. Multiple meta-analyses combining available RCTs all document a decrease in the percentage of subjects avoiding any rescue opioids, incidence of nausea, and incidence of vomiting [1,106,113,114].

Furthermore, paravertebral blocks result in a shorter hospital stay, although the difference may not be clinically significant. In six RCTs [86,98,106,109,111,116], the standard mean difference in length of stay was 36 minutes (SMD = -0.60 hour, 95% CI = -1.13 to -0.6, P = -0.028) [1]. The time difference was more clinically meaningful in two retrospective comparative studies. One demonstrated that patients who had received paravertebral blocks were more than twice as likely to be discharged on the day of surgery (28% vs. 11%) [12]; and, the other found that for patients with extensive breast surgery, the use of single-injection paravertebral blocks resulted in a decreased rate of overnight stays (61% paravertebral block vs. 97% GA, $P = 0.00001$) [109]. However, due to unidentified confounding variables and possible investigator bias, this data should be considered hypothesis-generating and not testing. Thus, further investigation is warranted. Lastly, there is evidence that satisfaction with pain control is improved with the addition of a paravertebral block [111,118,119].

Paravertebral Blocks: Complications

Overall, the reported complication rate for paravertebral blocks is relatively low, with the main serious complications being pneumothorax and hypotension, with incident rates of approximately 0.1–0.5% and 2–5%, respectively [1,12–16,40,57,58,79,84–86,98,101–106,109,111,115,116,120–125]. All complications resolved within 24 hours of surgery and there were no long-term sequelae noted. However, the success rate varies considerably among studies, from 90% to close to 100% [13]. A suggestion to improve the safety profile of paravertebral block by restricting placement in patients with a body mass index of < 25 kg/m2 (133), though logical, is not practical in today's society where a third of adults in the United States is obese (defined as a body mass index greater than or equal to 30) [126]. Use of an ultrasound for block placement may also contribute to an improved success rate and safety profile, but currently no evidence exists to support this claim [96,97].

Paravertebral Blocks: Continuous Infusion

Although single-injection blocks have been reported to provide analgesia for up to 72 hours [13], a continuous paravertebral block is far more reliable when the desired duration of action is longer than 12–16 hours [12,13,15,16,101,106,112,118,125,127,128] or at multiple levels [12,13,111,115]. Furthermore, paravertebral block catheters can be successfully managed in either an inpatient or outpatient setting [112,129,130]. There is mixed evidence regarding the impact of single-injection versus continuous paravertebral blocks, with two RCTs revealing little difference [14,129]; and, a third finding that continuous paravertebral blocks decrease pain, opioid requirements, and pain-related physical and emotional dysfunction during the perineural infusion [112]. Differences in the specific surgical procedures and/or analgesic protocols may account for the conflicting results [131].

Paravertebral Block: Adjuvants

The addition of clonidine (75 μg) to a long-acting local anesthetic can both improve analgesia and reduce opioid consumption for up to 72 hours following breast surgery [132]. Similarly, the addition of fentanyl to paravertebral local anesthetic improves analgesia, although it remains unclear if a proportionate improvement would result from simple peripheral administration [1,108,128].

Paravertebral Blocks: As Primary Anesthetic or Combined with TIVA

Paravertebral blocks, when used as the sole anesthetic, may yield advantages such as improved pain relief, decreased opioid consumption, decreased incidence of postoperative vomiting and shorter hospital stay, when compared to general anesthesia [15,86,98,102,111]. Combining paravertebral blocks with total intravenous anesthesia (TIVA) may further enhance the regional anesthetic benefits detailed previously [98]. The combination results in improved postoperative analgesia, opioid requirements, and shorter recovery room stays [98]. Additionally, lower rates of postoperative nausea and vomiting, decreased length of stay and improved quality of recovery at both hospital discharge and on postoperative day 2 may be seen [98]. Therefore, paravertebral blocks—alone or in conjunction with a total intravenous anesthetic—provide improved postoperative analgesia resulting in multiple benefits, including a faster time to recovery.

Paravertebral Blocks: Compared to Other Analgesic Techniques

When compared with direct local anesthetic wound infusion following modified radical mastectomy, single-injection paravertebral blocks provide superior analgesia and decrease pain-restricted movement during the

duration of the ropivacaine 0.5% block [133]. However, following the paravertebral block resolution, these findings were reversed with subjects undergoing local anesthetic infusion directly into their wounds experiencing less pain and pain-restricted movement. Such findings demonstrate the analgesic potency of paravertebral blocks, but also the limitation of the single-injection technique following surgical procedures resulting in significant postoperative pain of more than 8–12 hours in duration. It is important to ensure that patients with a paravertebral block/infusion are prepared with alternative analgesics for block offset, or else rebound pain may ensue [100].

A second RCT compared a continuous paravertebral block with local anesthetic wound infiltration following breast surgery; and, although the group with a nerve block reported pain scores 50% less than the infiltration group, the difference was not statistically significant [134]. However, this study was powered to detect a difference between means of 1.5 on a 0–10 pain scale, and presumed a standard deviation of only 1.5. Since more than 50% of subjects had a lumpectomy as opposed to a mastectomy, the baseline pain scores were so low that it would have been impossible to detect a difference in means of 1.5. Thererfore, the "negative" findings of this grossly underpowered study that tested for superiority are terribly misleading. Rather than demonstrating equivalency of the two treatments as implied by the authors, this investigation is an example of the importance of applying a potent—yet invasive—analgesic technique like a paravertebral block only when the surgical procedure results in pain warranting the potential risks of the modality [131].

Thoracic Epidural

A thoracic epidural local anesthetic infusion has profound and well-documented benefits for patients having major breast surgery. Data from one RCT demonstrates that the addition of a 48-hour thoracic epidural *dramatically* decreases pain, rescues analgesic use and opioid-related side effects such as nausea and vomiting, and increases patient satisfaction [135]. In addition, subjects with an epidural were ready for recovery room discharge in far less time than controls [135]; and, one retrospective investigation suggests that thoracic epidurals can decrease the time until hospital discharge as well [17]. A subsequent RCT involving mastectomy with immediate transverse rectus abdominis (TRAM) flap breast reconstruction similarly reported that the use of an epidural infusion with both local anesthetic and morphine dramatically improved analgesia and decreased the time until actual discharge to 101 hours from 126 hours in controls [136]. While never directly compared, the available evidence suggests that a thoracic epidural provides superior analgesia following major breast surgery compared with any other analgesic modality, including continuous paravertebral blocks. However, limitations of this technique include its use solely within the hospital—limiting its use in an era of same-day or over-night stay mastectomy—and, sympathectomy-induced hypotension.

Brachial Plexus Blocks

In a single RCT, bupivacaine or saline were administered directly to the brachial plexus (15 mL, infraclavicular location) and the intercostal spaces (5 mL each) prior to wound closure by the surgeon under direct visualization [137]. Fewer subjects receiving active medication required rescue analgesics within the first 24 postoperative hours (55%) compared with the control group (91%). However, pain scores and doses of rescue analgesics were not provided, making interpretation of the results problematic, at best. Importantly, it remains unknown (1) if a percutaneous infraclavicular brachial plexus block—as often performed for hand/forearm surgery—would result in equivalent results; and, (2) if the differences between treatments resulted from the brachial plexus block, the intercostal blocks, or a combination of the two. Due to these issues as well as a complete dearth in the decades since its publication in 1983 of other publications involving infraclavicular blocks for breast surgery, this technique cannot currently be recommended for standard clinical care.

Similarly, there is limited data suggesting that, compared with a control group, subjects randomized to a percutaneous interscalene brachial plexus block with bupivacaine (30 mL) experienced less pain and nausea; and, required less rescue morphine and antiemetic medication in the first 12 hours after radical mastectomy [138]. Of note, following the third postoperative hour, pain scores in the control group were less than 2 on a 0–10 scale, suggesting that the differences between 4 and 12 hours—while statistically significant—might not be considered clinically significant. As this single RCT demonstrates a pain score difference (which may not be clinically significant) in patients with an interscalene block, additional research in this area appears warranted.

Cervical Epidural

A cervical epidural local anesthetic (with or without an opioid) infusion may also be used to provide intraoperative anesthesia and postoperative analgesia for major breast surgery [139–143]. The selection of a cervical level catheter insertion—usually between the C7 and T1 vertebrae—is based on the fact that the pectoralis muscle is innervated from the brachial plexus (C5-C8) [144], and was encouraged by a prior report that a cervical epidural block provides better sensory block for thoracic procedures than a high thoracic epidural block [145]. Unfortunately, this technique has been neither validated nor compared with other techniques with an RCT; and case reports and small series of patients do not allow for an accurate estimation of the potential risks, either absolute or relative to other modalities. Therefore, while the initial reports are intriguing and suggest that further research is warranted, there is little

data on which to base a recommendation for its clinical use at the time of this writing.

Interfascial Plane Blocks

Several types of interfascial plane blocks have been described specifically for breast surgery. The Pecs I block was first described in 2011 within a Letter to the Editor, with local anesthetic deposited in the plane in which the pectoral nerves are found between the pectoralis major and minor muscles [146]. The subsequent year, a modified version of this approach named the Pecs II block was described for axillary dissections by aiming to increase the number of nerves affected to include the intercostobrachial, intercostal 3-6, and long thoracic nerves [147]. Variant approaches have been published [148,149], including the insertion of a catheter to allow a postoperative perineural local anesthetic infusion [150]. The technique has been described primarily for breast augmentation [148,149], with one retrospective series reporting decreased pain scores at 8 hours when a pectoralis block was added to a paravertebral block compared with historic controls with solely a paravertebral block [151]. However, the only available RCT involves radical mastectomy procedures in which subjects were randomized to receive either a general anesthetic or a general anesthetic plus combined Pecs I and II blocks with 0.25% bupivacaine [152]. Subjects with the regional blocks reported pain scores approximately 50% lower than the controls during the first 24 postoperative hours; required far less opioid within the first 12 hours; experienced less nausea, vomiting, and sedation within the recovery room; and were discharged earlier from both the recovery room and hospital. This study involving 120 subjects reports such a dramatic improvement in both analgesia and analgesia-related benefits with the Pecs I and II blocks that it warrants replication as well as future comparisons single-injection and continuous paravertebral nerve blocks, as well as thoracic epidural infusion. There is currently very little randomized, controlled data on which to base recommendations for the Pecs blocks—especially relative to paravertebral and epidural analgesics—but, if future investigation confirms the initial reports, these blocks would be considered the gold standard for breast surgery due to their relative ease of insertion and theoretically low risk of complications.

An additional interfascial block was recently described (2015) termed the transversus thoracic muscle plane block in which local anesthetic is injected between the transversus thoracic muscles to block the anterior branches of intercostal nerves T2-T6 innervating the internal mammary region [153–155]. In a case series of three patients, the combination of a transversus thoracic muscle plane block and a Pecs II block allowed for breast cancer resection without the use of general anesthesia [154]. The benefits, risks, and usefulness either alone or in conjunction with other peripheral nerve blocks of this newly described block have yet to be elucidated, and require future investigation.

Interpleural Blocks

Interpleural blocks can also provide post-mastectomy analgesia through the somatic block of multiple thoracic dermatomes [156,157]. Local anesthetic is deposited between the parietal and visceral pleura [158–160], where it then diffuses to the subpleural space and the intercostal nerves [159–161]. In one RCT comparing single-injection interpleural and single-level paravertebral blocks (both bupivacaine 0.5%) for patients undergoing mastectomy, pain scores and analgesic consumption were similar for both interventions [161]. Both treatment groups also exhibited decreased lung functions on the first postoperative day, which improved to near-normal levels by the second postoperative day. Risks of this procedure include pneumothorax, intravascular injection, and intra-bronchial infection [159,160]. Similar to the Pecs blocks, there is extremely little data involving interpleural blocks on which to base recommendations regarding breast surgery anesthesia and analgesia.

Persistent Post-Surgical (Chronic) Pain

Persistent post-surgical pain lasting over 3 months is a common complication following breast surgery [162], with a reported incidence between 20% and 68% [163–166]. The variance may be attributed to multiple factors, including differences in definition and the type of breast cancer surgery treatment involved.[5] The pain itself, mostly neuropathic in nature, is often described as burning, shooting, pressure, numbness, or phantom [162,165–167]; and is described as “severe” in 10% of patients [8,168]. Reported to occur in the axilla, chest wall and proximal medial arm or shoulder [53,162,169,170], the pain may extend beyond the area of the mastectomy, and is strongly correlated with depression and anxiety [171].

Preoperative risk factors associated with persistent pain following breast surgery include depression [172], anxiety [173], pain in any anatomic location [174], young age [4,8,165,175–181], and genetics [5]. Intraoperative risk factors include axillary staging and lymph node dissection [8,175,182–184]. The contribution of intercostobrachial nerve injury to chronic pain remains unclear [5], with three retrospective investigations identifying this as a risk factor, while 4 RCTs concluded otherwise [110,185–189]. Postoperative risk factors include radiation therapy [4,8,110,190,191] and increased severity of pain in the immediate postoperative period [4,191,192]. Evidence of post-surgical complication—for example, infection, seroma, hematoma, axillary web syndrome, etc.—contribution is mixed, with only one in four investigations finding an association with chronic pain [179,191–193].

Although the evidence is somewhat mixed, there is some evidence that decreasing pain acuity in the immediate postoperative period decreases the incidence and

severity of persistent post-surgical pain following breast procedures. An example of the mixed nature of the evidence may be found in the perioperative administration of diverse medications such as mexiletine, venlafaxine, gabapentin, ropivacaine, and a eutectic mixture of local anesthetics cream that all improve postoperative analgesia, yet subsequently either fail [53,194,195] or succeed [196,197] in reducing the incidence of chronic pain following mastectomy. Also demonstrating the complexity of this issue, multiple short term interventions fail to result in a meaningful/measurable reduction in acute postoperative pain, yet appear to decrease the risk/intensity of persistent post-surgical pain, including perioperative cutaneous application of an eutectic mixture of local anesthetic cream [198] and intravenous infusion of lidocaine [199].

However, more consistency may be found regarding paravertebral nerve blocks for major surgical procedures of the breast. One RCT provided evidence that a single-injection paravertebral block with bupivacaine decreases pain scores and opioid requirements within the first 24 postoperative hours [16], as well as the incidence of subsequent severe pain after 1, 6, and 12 months [110]. And three RCTs reported that a 48–72-hour continuous paravertebral nerve block decreased pain (and in some cases pain-related emotional and physical disability) both during the local anesthetic perineural infusion as well as 2.5, 6, and 12 months following surgery [103,110,200]. A single RCT comparing single-injection paravertebral nerve blocks and wound infiltration failed to detect a difference between treatments at 12 months, and unfortunately did not report any pain data prior to the 12-month time point [201]. Of note, this investigation was terminated early due to futility because both treatment groups experienced such a low incidence of chronic pain (8%) that detecting the prospectively-defined minimal difference of 20% was impossible. It remains unknown if the two groups had little pain simply due to non-intervention factors (e.g., surgical technique), or because both treatments decreased chronic pain equivalently. Regardless of the underlying etiology, this study's negative findings do not contradict the three positive RCTs demonstrating that a continuous paravertebral block reduces both the incidence and intensity of persistent post-surgical pain [103,110,200].

Conclusions

Decreasing postoperative pain—both acute and chronic—is of paramount importance for patients undergoing surgical procedures of the breast. To date, the related research is extensive, but not declarative, with conflicting studies and a lack of data derived from RCTs often obfuscating the picture. Nevertheless, clinicians have a body of data on which to base their treatment decisions. The evidence regarding preemptive ketamine, scheduled opioids, perioperative NSAIDs, and intravenous lidocaine is mixed and deserves further investigation. There is strong evidence that both pregabalin and gabapentin provide analgesic benefits following breast surgery. There is minimal and conflicting data from high-quality randomized, controlled studies suggesting that directly infiltrating and/or infusing local anesthetic (liposome encapsulated or unencapsulated) into the surgical wound is a reliably effective analgesic. In contrast, there is a plethora of data demonstrating the potent analgesia, opioid sparing, and decreased opioid-related side effects from thoracic epidural infusion and both single-injection and continuous paravertebral nerve blocks (the latter two demonstrating decreased persistent post-surgical pain between 2.5 and 12 months). Techniques with limited—yet promising—data deserving additional investigation include brachial plexus blocks, cervical epidural infusion, interfascial plane blocks, and interpleural blocks.

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