Title

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Journal

Pain Management, 6(6)

ISSN

1758-1869

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Publication Date

2016-11-01

DOI

10.2217/pmt-2015-0008

Peer reviewed

REVIEW

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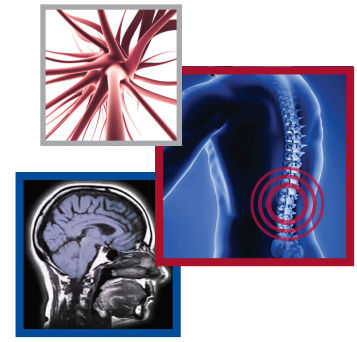
Pain Management



A review of postoperative analgesia for breast cancer surgery

Gloria S Cheng[1] & Brian M Ilfeld[*,2,3]

Practice points

- Scheduled opioids may decrease the need for rescue analgesics, but may also result in more postoperative nausea and vomiting.
- Preoperative dosing of antiepileptics (i.e., gabapentin and pregabalin) improves postoperative analgesia and decreases supplemental analgesic requirements.
- Intravenous lidocaine infusion does not appear to confer significant analgesic benefit.
- The benefit of wound infiltration is minimal. In addition, pre-incision infiltration does not seem to lessen postoperative analgesic requirements.
- Wound infusion catheters may provide minimal analgesic benefit, but additional research is required to draw conclusions.
- There are currently little high-quality data to suggest that liposomal bupivacaine infiltration for breast surgery reduces postoperative pain, although additional research is required before drawing conclusions.
- Paravertebral blocks are reported to decrease pain scores, postoperative opioid consumption as well as opioid-related side effects and improve patient satisfaction. Single and multiple level blocks have inherently opposing risks and benefits: improved coverage versus increased complications. Results from studies comparing single injection to continuous infusion is varied, requiring additional research to draw conclusions.
- Data on thoracic epidurals consistently report beneficial analgesic outcomes, but the procedure is limited by the potential for complications and its incompatibility with an outpatient setting.
- Studies on brachial plexus and cervical epidural blocks are limited or lacking, respectively; but, techniques hold promise and require future investigation.
- Interfacial and interpleural blocks are more recently described regional techniques for breast cancer surgery and deserve further study. These blocks provide promising alternatives to the paravertebral and thoracic epidural.
- Chronic or persistent postsurgical pain is a significant and common problem after breast cancer surgery. There are limited data that paravertebral blocks/infusion in the immediate preoperative period may attenuate chronic pain.

An online database search with subsequent article review was performed in order to review the various analgesic modalities for breast cancer surgery. Of 514 abstracts, 284 full-length manuscripts were reviewed. The effect of pharmacologic interventions is varied (NSAIDS, opioids, anticonvulsants, ketamine, lidocaine). Likewise, data from high-quality randomized, controlled studies on wound infiltration (including liposome encapsulated) and infusion of local anesthetic are minimal and conflicting. Conversely, abundant evidence demonstrates

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paravertebral blocks and thoracic epidural infusions provide effective analgesia and minimize opioid requirements, while decreasing opioid-related side effects in the immediate postoperative period. Other techniques with promising – but extremely limited – data include cervical epidural infusion, brachial plexus, interfascial plane and interpleural blocks. In conclusion, procedural interventions involving regional blocks are more conclusively effective than pharmacologic modalities in providing analgesia to patients following surgery for breast cancer.

First draft submitted: 13 February 2016; Accepted for publication: 4 May 2016; Published online: 2 August 2016

KEYWORDS
- breast cancer
- mastectomy
- paravertebral
- postoperative pain
- thoracic epidural

Breast cancer is the most common, nonepidermal cancer in women [1]. Every year, over 230,000 new cases are diagnosed every year in the USA [2]. Surgery is a primary form of treatment [3], but 40% of women who undergo breast cancer surgery experience acute postoperative pain and up to 60% develop persistent pain after surgery [4–8]. Methods used to control pain include pharmacological analgesics, both oral and intravenous, as well as more invasive techniques utilizing local anesthetics, such as local anesthetic infiltration [9,10], intercostal block [11], thoracic epidural anesthesia [12] and paravertebral block [13–17]. This article is a review of the published literature regarding perioperative pain control following breast cancer surgery.

Methods

The online databases, PubMed, Scopus and Google Scholar, were interrogated for abstracts involving the treatment of pain following surgery for breast cancer. Search terms related to analgesia for breast cancer surgery ('mastectomy', 'breast neoplasms', 'surgical procedures', 'analgesia') were used. Studies, case reports and meta-analyses of interest were then further reviewed in full, and additional publications of interest were identified within their reference lists, and those articles reviewed.

Results

A total of 514 abstracts were reviewed, with 284 studies meeting criteria for full review.

• Pharmacologic

NSAIDs

Many studies exist on the analgesic use of NSAIDs for multiple surgical procedures; however, only a few RCTs focus on their use for breast cancer surgeries. In one study, researchers randomized subjects having mastectomy to either rectal diclofenac (50 mg), an NSAID, or placebo every 8 h for three doses [18]. Similar to studies looking at other surgical procedures, the patients that received the NSAID experienced less pain at rest (although no significant difference was noted with motion) and required 30% less opioid rescue analgesics. However, those patients that received diclofenac also had a significantly higher rate of postoperative bleeding ($p < 0.01$) [18]. As part of a multimodal pain regimen, NSAIDs may be a beneficial adjunct, but should be used with caution as they may increase the risk of postsurgical bleeding.

Opioids

The scheduled use of perioperative opioids for breast surgeries has varied outcomes. Rather than evaluating the use of opioids titrated to pain score after surgery, two randomized, controlled trials (RCTs) examined the effect of scheduled administration – dosing without regard to pain level – on postoperative pain scores and the need for additional opioids [19,20]. In the first study, two doses of either oral controlled-release oxycodone (20 mg) or placebo were given to the patient; the first dose 1 h before mastectomy and the second dose given 12 h after the first. Unsurprisingly, the patients in the treatment group required less supplemental opioids and reported lower pain scores within the first 24 postoperative hours, without any difference in opioid-related side effects. In contrast, subjects in another RCT were randomized to receive either sustained-release tramadol (100 mg) or placebo administered 1 h prior to surgery with a second dose 12 h later, and minimal difference was seen in either postoperative pain scores or opioid consumption [20]. In addition, those in the treatment group reported more nausea and vomiting. More studies should be done to elucidate the impact of scheduled opioids on patients undergoing breast surgeries.

Antiepileptics

Although originally developed as anticonvulsant medicines, pregabalin and gabapentin can play

a pharmacologic role in treating neuropathic pain [21,22]. Their effectiveness in reducing pain scores and postsurgical analgesic requirements are reported for various surgical procedures, including spinal surgery [23], nephrectomy [24] and hysterectomy [25,26]. They demonstrate a similar efficacy when used for breast surgeries [27]. In one RCT, one preoperative dose of gabapentin (1200 mg) was associated with a decreased postoperative morphine requirement and decreased pain with movement for up to 4 h postoperatively [27], with no difference in side effects noted. However, pain at rest was similar between the two groups. In a related study, pregabalin (75 mg) administered twice daily for seven days in patients undergoing augmentation mammoplasty, reported a significantly decreased postoperative opioid requirement [28]. Similarly, subjects who underwent mastectomy were randomized as part of an RCT to receive two doses of either pregabalin or placebo – one dose an hour before surgery and the second dose 12 h later [29]. The treatment group reported decreased pain at rest at 1, 24 and 48 h postoperatively. Lastly, a study reported that a single 600 mg dose of preoperative gabapentin, when compared with placebo, resulted in significantly less opioid requirement morphine consumption as well as longer time to first postoperative analgesic dose [30]. Additionally, those who received gabapentin reported decreased pain, both at rest and with movement, for most time periods up to 12 h after surgery; all without significant side effects. Consistent evidence gathered from multiple studies supports the analgesic benefits of gabapentin and pregabalin following breast surgery.

Ketamine

Ketamine, an NMDA receptor inhibitor, can be used for perioperative analgesia. Limited data exist on its specific use for surgical procedures of the breast; but, expanding on the concept of preemptive analgesia [31,32], one RCT theorized: ketamine, if given preoperatively, could decrease postoperative pain [33]. Patients undergoing mastectomy were randomized to receive a single dose of ketamine (0.15 mg/kg intravenously) either preoperatively or postoperatively. The group that received the dose after surgery was finished reported a decreased narcotic requirement for the first 2 h after surgery, consistent with ketamine's duration of action. However, no data supported the use of ketamine as a preemptive analgesic.

Intravenous lidocaine

Intravenous lidocaine, despite reported analgesic benefits for neuropathic pain [34] and abdominal and thoracic surgeries [35–39], seems to provide minimal analgesic benefit when used for breast surgery [40–42]. In one RCT involving patients undergoing mastectomy, there was no significant difference reported in either pain scores or postoperative analgesic use between patients that received an intraoperative infusion of intravenous lidocaine (3 mg/kg) and those in the placebo group [43]. In a comparable RCT composed of subjects undergoing breast plastic surgery, no significant difference in length of stay, patient satisfaction with pain control, postoperative pain, time to return of bowel function and side effects was reported when comparing a cohort that received intravenous lidocaine (1.5 mg/kg/h) to a placebo group [44]. Similarly, in a third RCT, an intravenous lidocaine infusion (bolus 1.5 mg/kg at induction followed by 2 mg/kg/h infusion) did not significantly impact opioid consumption, pain score, rate of PONV or fatigue, when compared with the placebo group [42]. It is unclear why results starkly differ between other types of surgeries and breast surgeries. The impact of perioperative intravenous lidocaine on persistent postsurgical pain is presented later in this paper.

• Local anesthesia

Wound infiltration

A minimally invasive anesthetic technique is directly infiltrating local anesthetic into the surgical wound. Part of this technique's appeal is its avoidance of risks inherent to other invasive analgesic procedures, such as pneumothorax, pleural puncture and high-volume intravascular injection. Regrettably, minimal data from high-quality RCTs support its use as an effective analgesic [45]. Six RCTs found a minimal decrease in pain scores that only attained statistical significance for a few postoperative hours [46–51]; 15 RCTs were unable to find any statistically significant analgesic benefit at all [9–10,46–58]. Moreover, a meta-analysis that combined 13 of the trials with a total of 1150 subjects found only a minimal incremental improvement in pain scores at 2 h ($p = 0.05$), with no ensuing benefit reported [59].

Nonetheless, other benefits of the wound infiltration have been reported, despite its nominal analgesic value. However, because these 'benefits' were identified in secondary

end points, statistical corrections for multiple comparisons were not made. As an example, one RCT (n = 79) comparing wound infiltration with 0.25% bupivacaine to placebo in subjects scheduled for various types of breast procedures, found that the pain score – the primary end point – was low in both groups, with no statistical difference between the two. However, subjects in the treatment groups required 2.9 mg less opioid within the first 24 postoperative hours (bupivacaine 3.4 mg vs control 7.3 mg; p = 0.02) [53]. Unfortunately, because there are over 15 statistical comparisons, there is an unacceptably high risk of an erroneous false positive (type 1 error). Nevertheless, opioid use is only a surrogate end point, with opioid-induced side effects being the clinically significant outcome. Currently, no RCTs have shown wound infiltration to decrease any non-surrogate outcomes. Minimal data exist in the current literature to indicate that a patient's postsurgical experience is improved by wound infiltration.

In addition, wound infiltration given preincision has not been shown to decrease analgesic requirement in the immediate postoperative period. When comparing local anesthetic infiltrated into the wound before incision with infiltration after incision in an RCT, postoperative pain was not significantly different between the groups [60]. In a subsequent RCT, the addition of a placebo arm was added into the study design [48], in another attempt to look for a preemptive analgesic effect [61]. This study demonstrated that wound infiltration with local anesthetic provided improved postoperative analgesia and a decreased opioid requirement, but whether the infiltration occurred before or after surgery mattered little. Moreover, similar to in the previous paragraph, the placebo group, despite requiring increased opioids, did not report an increase in opioid-related side effects, such as nausea, vomiting or anti-emetic requirement [48]. In conclusion, wound infiltration performed prior to incision does not lessen the postoperative analgesic need.

Wound infusion

The placement of a catheter directly into the wound allows for continuous infusion of local anesthetic postoperatively. Whether these catheters provide analgesic benefit after breast surgery remains unclear. In one RCT consisting of patients undergoing radical mastectomy [62], all subjects received levobupivacaine 0.25% (30 ml) as a direct wound infiltration, and a percutaneous wound infusion catheter. The patients were randomized to receive either additional levobupivacaine (0.5%) or saline (2 ml/h) for 48 h via infusion through the wound catheter. The patients in the levobupivacaine group reported lower pain scores up to 48 h postoperatively, as well as a decreased analgesic requirement. However, the disparity in the groups is unexpected, as both groups received a levobupivacaine 0.25% (30 ml) infiltration at the end of surgery, which makes it more difficult to interpret the remainder of the study results. A meta-analysis of 4 RCTs were unable to identify a significant difference between local anesthetic and placebo infusion at any time point after breast surgery (which included both mastectomy and mammoplasty procedures) [63].

The abdominal pain felt after breast reconstruction with a transverse rectus abdominis myocutaneous (TRAM) flap or deep inferior epigastric perforator flap can be substantial. A pilot study (n = 17) involving patients undergoing TRAM flap, revealed patients that received a continuous wound infusion of local anesthetic after surgery showed a trend toward better pain relief at rest, with coughing at 8 h postoperatively, and experienced a quicker return of bowel function, when compared with a placebo infusion [64]. The positive effect was not statistically significant, but was convincing enough to prompt further study. In a subsequent meta-analysis, that included two randomized controlled [65,66] and three retrospective, nonrandomized [67–69] studies of patients undergoing free lower abdominal flap breast reconstruction surgery with wound catheters identified a significant decrease in opioid requirement [70]. Of note, pain scores were not analyzed and no significant difference was seen in other outcomes, such as administration of anti-emetics or duration of hospital stay. In conclusion, wound catheter infusions with local anesthetic for breast cancer surgeries may yield minimal clinical advantage, but is an area that deserves further study.

Liposomal bupivacaine

A long-acting local anesthetic routinely used for wound infiltration after breast surgery is bupivacaine HCl [71–73]. Its duration of action as noted in multiple surgery types is approximately 12 h [74–76]. As an extension of its duration would extend its benefit, a depot formulation of bupivacaine was developed. As a

liposomal formulation, it would allow for the slow, continuous release of local anesthetic over a period of day [77–79]. In a nonrandomized, retrospective, unmasked study looking at its use in breast reconstruction patients, the liposomal formulation was shown to be of significant benefit when compared with bupivacaine or placebo infusion; including decreased pain scores up to 24 h postoperatively, and shorter hospital length-of-stay [80]. It is suggested that the liposomal bupivacaine can exert a beneficial effect for up to 72 h [81]. A pooled data analysis that includes nine double-blind studies involving multiple surgery types, including breast augmentation surgery, concluded that patients injected with liposomal bupivacaine reported lower cumulative pain scores (through 72 h) than those injected with bupivacaine HCl [82]. However, in other randomized, bupivacaine HCl-controlled trials, no significant benefit was noted, except for decreased opioid consumption through 48–60 h [83,84]. As there is a lack of evidence from RCTs supporting liposomal bupivacaine as significantly advantageous to bupivacaine HCl, and as the cost of the newer formulation is drastically higher than the original, further studies are needed before commonplace use of the liposomal formulation is advised. Of note, of the nine RCTs that compared the two bupivacaine formulations for various surgeries including breast surgery, the only one that reported improved analgesia involved hemorrhoidectomy [84–87].

• Regional anesthesia

Paravertebral nerve blocks

A thoracic paravertebral block is type of regional anesthetic technique that provides ipsilateral analgesia of the chest and abdomen. Local anesthetic is injected into a space adjacent to a thoracic spinal nerve as it emerges from the intervertebral foramen [88]. The heads of the ribs form the superior and inferior boundaries; the superior costotransverse ligament forms the posterior boundary; the parietal pleura creates the anterolateral boundary, and the vertebrae and intervertebral foramina establishes the medial boundary [89]. Initially described in the early 20th century, the block gained peak popularity over the next two decades, then experienced a resurgence in use in the recent past [88]. Unilateral and bilateral thoracic paravertebral blocks can provide analgesia and anesthesia for breast surgery and may be performed at one, or more than one vertebral levels [90]. A single injection block may be more comfortable for the patient due to fewer injections, requiring less sedation and improving patient satisfaction [17,91]. Blocking multiple thoracic levels may increase the number of affected dermatomes, thereby improving analgesia duration and quality, but the increased number of needle passes exposes patients to a higher risk of complications [14,92–94]. Published data directly comparing the two techniques for breast cancer surgery analgesia is lacking at this time. In its absence, a meta-analysis involving 24 studies [1] that includes both single and multiple level techniques concluded that the use of multiple-level blocks resulted in decreased pain with movement 2, 48 and 72 h after surgery, when compared with single-level blocks. However, no difference was seen in pain at rest between the two groups. This meta-analysis also found that though multiple injections are associated with a higher incidence of vascular puncture, the risk is mitigated by the use of ultrasound. The use of ultrasound in block placement is recommended. Though the meta-analysis reported that ultrasound guidance yielded no effect on efficacy, its use was associated with fewer complications. 3D ultrasound can be used to visualize the paravertebral space and surrounding structures, but as its use has not yet been described for clinical application and block placement, recommendations on its use do not currently exist [95].

An ample body of evidence exists to support the analgesia and opioid-reducing effect that can result from paravertebral blocks placed for breast surgeries. Studies involving single-injection and/or continuous paravertebral nerve blocks demonstrate statistically significant reductions in pain scores at rest as well as with movement at 2 h [1,14–17,91,94,96–105], 24 h [1,14–16,96,97,99–103,105–110], 48 h [1,14–15,96,101,103,109] and up to 72 h after surgery [1,14–15,101,103,109]. The results of three independent meta-analyses similarly concluded that paravertebral blocks, when compared with opioid analgesics alone, can reduce both average and worst pain scores by approximately 1.7–2.5 points on a 0–10 scale [104,111–112].

Paravertebral blocks: extending duration

Clonidine (75 µg), used as an additive to a long-acting local anesthetic, can prolong the analgesic block effect can both for up to 72 h after breast surgery [113]. Likewise, fentanyl added to local anesthetic for paravertebral block also improves analgesia, though it is uncertain if a similar improvement could also occur with

simple peripheral administration [1,106,114]. It is important to remember that analgesics should be available for the patient when the block wears off, as rebound pain can occur [98]. Also, surgical selection is vital, as the analgesic effect of paravertebral blocks is most notable with postoperative pain too significant for oral analgesics to treat well [115].

Although, a single-injection paravertebral block can provide analgesia for up to 72 h [14], utilizing a continuous paravertebral block is a more reliable way to extend block duration for more than 12–16 h [13–14,16–17,99,104,110,114,116–118]. In addition, paravertebral block catheters can be managed in either an outpatient or inpatient setting [110,119–120]. The existing evidence on the impact of continuous paravertebral blocks versus single-injection blocks is controversial; two RCTs reveal minimal difference [15,119] and a third found that continuous paravertebral blocks decreased pain, opioid requirements, and pain-related physical and emotional dysfunction for the duration of the infusion [110]. The conflicting results may result from differences in the specific surgical procedures and/or analgesic protocols [115].

Paravertebral blocks: advantages

Benefits directly extending from the improved analgesia offered by paravertebral blocks include decreased opioid consumption, decreased opioid-related side effects and increased patient satisfaction. Four independent meta-analyses [1,104,111–112] report opioid sparing, though the significance of that benefit varies widely between studies, likely as a result of differences in patient population, treatment techniques, surgical procedures and supplemental medications. It stands to follow that decreased opioid-related side effects, such as postoperative nausea and vomiting, are also reported by multiple RCTs to be decreased with the use of paravertebral blocks [1,13,16,17,93,94,96,100,102,104–106,109,112,121–123]. Similar to the impact on opioid sparing, the amount of risk reduction widely varies – with a few studies reporting no statistically significant difference between treatments [98] – again, likely a result of differences in patient population, treatment techniques, surgical procedures and supplemental medications. Multiple meta-analyses evaluating available RCTs all report a decrease in the percentage of subjects requiring rescue opioids, incidence of nausea and incidence of vomiting [1,104,111–112].

Moreover, paravertebral blocks are associated with shorter hospital duration, though the clinical significance may be limited. The standard mean difference in length of stay from six RCTs [91,96,104,107,109,122] was 36 min (SMD: -0.60 h; 95% CI: -1.13 to -0.6; p = -0.028) [1]. Data from two retrospective comparative studies bear more clinical significance: in one, patients who with paravertebral blocks were twice as likely to be discharged on the day of surgery (28 vs 11%) [13]; in the other, patients with paravertebral blocks for extensive breast surgery had a decreased rate of overnight hospital stays (61% paravertebral block vs 97% GA, p = 0.00001) [107]. However, unidentified confounding variables and possible investigator bias may cloud the picture, and these data should be used as hypothesis generating and not hypothesis testing exercises. Thus, further investigation is warranted. Lastly, paravertebral blocks improve patient satisfaction with pain control [109,117,124].

Paravertebral blocks: adverse events

The most serious complications specific to paravertebral blocks are pneumothorax and hypotension. Fortunately, the reported rate of these adverse events is low, with incident rates of approximately 0.1–0.5% and 2–5%, respectively [1,13–17,43,60,61,88,91,93–94,96,99–104,107,109,118,121,122,125–129]. In all instances, the complications resolved within 24 h with no long-term sequelae noted. The success rate of paravertebral blocks ranges from 90 to close to 100% [14]. To increase the safety of paravertebral block placement, consider adhering to the following recommendations: minimize placement in patients with BMI <25 kg/m^2 [128], and adopt an ultrasound-guided placement technique [1,130]. Also consider that the placement of single-level blocks is associated with a decreased incidence of vascular puncture, when compared with multiple-level blocks [1].

Paravertebral blocks with TIVA

The combination of total intravenous anesthesia (TIVA) and paravertebral blocks may augment the benefits of a regional anesthetic technique. Improved postoperative analgesia, decreased opioid requirements and shorter recovery room stays have been described in multiple RCTs [16,91,96,100,109]. Additionally, it may lessen the incidence of postoperative nausea and vomiting, shorten hospital stay and improve quality of recovery [131] at both hospital discharge and

on postoperative day 2 [96]. In conclusion, there are many benefits to paravertebral blocks, when used in conjunction with a total intravenous anesthetic, including faster recovery time and improved pain control after surgery.

Paravertebral blocks versus other interventions

In comparing paravertebral blocks with direct local anesthetic wound infusion following modified radical mastectomy, the paravertebral blocks provided better analgesia and pain-restricted movement for the duration of the ropivacaine 0.5% block [132]. However, after the block wore off, the reverse occurred, with the patients that received the infusion reporting less pain and pain-restricted movement. This highlights the benefit of the paravertebral blocks, while serving as a reminder of the inherent limitation of the single-injection technique for surgical procedures that result in postoperative pain that extends for more than 8–12 h.

Another RCT compared continuous paravertebral block infusion with local anesthetic wound infiltration following breast surgery. The pain scores reported by the continuous paravertebral block group were lower than those by the infiltration group, but not enough to be statistically significant [133]. However, this result requires closer examination. As more than half of the patients in the study had a lumpectomy (vs mastectomy), the baseline pain scores were low. With such low baseline pain scores, it would have been nearly impossible to detect the difference between pain means necessary to reach statistical significance. As a result, this underpowered study appears to report 'negative' findings which may be misleading. This outcome emphasizes the importance of using paravertebral blocks for surgical procedures that result in enough postoperative pain that justifies and warrants the use of regional anesthesia techniques [115].

Thoracic epidural

The benefits incurred by a thoracic epidural local anesthetic infusion for patients undergoing major breast surgery are clear and well-documented. These benefits were demonstrated in an RCT which showed that the addition of a 48-h thoracic epidural infusion yielded positive findings, including substantially decreased pain, rescue analgesic consumption and nausea and vomiting, as well as increased patient satisfaction [134]. In addition, patients with an epidural met recovery room discharge criteria earlier than those in the control group [134]; time until hospital discharge may be decreased as well, based on results from a retrospective investigation [12]. Similar reports of improved analgesia and decreased narcotic use were reported in a subsequent RCT looking at epidural infusions used for mastectomy with TRAM flap breast reconstruction; additionally, time to discharge decreased by approximately 20% (101 vs 126 h) [135]. Though no direct comparison currently exists, the available evidence more consistently shows that a thoracic epidural after major breast cancer surgery provides postoperative analgesia, when compared with the current data on other available techniques, including continuous paravertebral blocks. Specific limitations to this technique include the necessity to stay in the hospital while the epidural is in place, the need for caution in using anticoagulants and the sympathectomy-induced hypotension. While these limitations may lessen the use of thoracic epidurals, its effectiveness should not be overlooked.

Brachial plexus blocks

In a single RCT involving patients undergoing mastectomy surgery, bupivacaine or saline was deposited around the brachial plexus (15 ml, infraclavicular location) and in the intercostal spaces (5 ml each) before the end of surgery, by the surgeon under direct visualization [136]. Far fewer patients from the treatment group required rescue analgesics, when compared with the control group. However, the lack of pain scores and doses of rescue analgesics makes it challenging to accurately interpret the results. Moreover, it is unclear if the difference between groups should be attributed to the intercostal blocks, the brachial plexus block, or the combination of the two. This ambiguity, combined with the lack of further studies on infraclavicular blocks for breast surgeries, keeps it from being a standard technique used for postoperative analgesia after breast surgery.

Similarly, limited data exist to suggest that subjects randomized to a percutaneous interscalene brachial plexus block with bupivacaine (30 ml) experienced less pain and nausea than the control group, requiring less rescue analgesics and antiemetic in the initial 12 h after radical mastectomy [137]. It is worth mentioning that after 3 h postoperatively, pain scores in the control group were very low (less than 2 on a 0–10 scale), suggesting that any difference in

pain between 4 and 12 h postoperatively, may not be clinically significant. Nonetheless, the results of this singular RCT are compelling, and indicate that a single-injection interscalene block may offer analgesic benefits after breast surgery.

Cervical epidural

A more cephalic epidural option is a local anesthetic infusion (with or without opioid) into the cervical epidural space. This regional technique may be used to provide intraoperative anesthesia and postoperative analgesia for major breast surgery [138–142]. As innervation of the pectoralis muscle is derived from the brachial plexus (C5–C8), it stands to reason that a catheter placed between the C7 and T1 vertebrae would offer analgesic benefit [143] and is supported by a prior report that a cervical epidural block delivers improved sensory block for thoracic procedures when compared with a high thoracic epidural block [144]. However, there are no RCTs that either validate or compare this technique to other analgesic procedures. By its nature, case reports and small series of patients that describe use of this technique do not provide an accurate risk assessment of this procedure. Consequently, though initial reports are interesting, further investigation is needed before a recommendation for its use can be given.

Interfascial plane blocks

Interfascial plane blocks of multiple varieties and approaches have been described specifically for breast surgery. The Pecs I block, first mentioned in 2011 in a letter to the editor, describes the placement of local anesthetic in the plane between the pectoralis major and minor muscles, where the pectoral nerves are found [145]. The first mention of the Pecs II block occurred a year later in 2012. A variant of the Pecs I block, it was created to expand anesthetic coverage to include the intercostobrachial, intercostal 3–6 and long thoracic nerves, in order to help with the pain of axillary dissections [146]. Modifications to the approach for the blocks have been published [147,148]; a catheter placed in the interfascial plane has also been described, to allow for a perineural local anesthetic infusion [149]. Mostly described for breast augmentation surgeries [147,148], a retrospective series reported decreased pain scores at 8 hours when a pectoralis block added to a paravertebral block was compared with a paravertebral block alone [150]. The only available RCT took patients undergoing radical mastectomy procedures and randomized them to either general anesthesia plus combined Pecs I and II blocks with 0.25% bupivacaine or general anesthesia alone [151]. The pectoralis block group reported a generally more positive recovery period: pain scores approximately 50% lower than the control group during the first 24 postoperative hours, significantly less narcotics usage within the first 12 h; less nausea, vomiting and sedation in the recovery room; and earlier discharge from both the recovery room and hospital. The overwhelmingly positive results in this study with 120 subjects merits further investigation to evaluate for reproducibility, as well as to compare with other analgesic methods currently used, such as single-injection and continuous paravertebral nerve blocks, and thoracic epidural infusion. The current amount of randomized, controlled data on pectoralis blocks are very limited, but if future studies corroborate with the initially affirmative findings, the blocks could well become the gold standard for alleviating pain after breast surgery, as they are relatively easy to place with a minimal risk of complications.

In 2015, another interfascial block, the transversus thoracic muscle plane block, was first described. This block anesthetizes the anterior branches of intercostal nerves T2–T6, which innervates the internal mammary region [152–154], by injecting local anesthetic between the transversus thoracic muscles. In a case series of three patients, this block, combined with a Pecs II block, provided surgical anesthesia for breast cancer resection, providing an effective substitute general anesthesia [153]. Due to its recent emergence as a nerve block, the literature on this technique is sparse. Evidence regarding its efficacy and risks will still need to be determined and revealed before recommendation for its use can be safely justified.

Interpleural and intercostal blocks

Interpleural blocks can help with breast mastectomy pain by somatic blockade to multiple thoracic dermatomes [155,156]. Local anesthetic that is placed between the visceral and parietal pleura [157–159] diffuses to the subpleural space and anesthetizes the intercostal nerves [158–160]. An RCT compared single-injection interpleural blocks to single-level paravertebral blocks (both bupivacaine 0.5%) in patients undergoing mastectomy, and demonstrated that there was no difference in pain scores and opioid requirements

between the two groups [160]. Both groups also reported decreased lung functions on the first postoperative day, which improved to near-normal levels by the next day. Specific risks of this procedure include intravascular injection, pneumothorax and intrabronchial infection [158,159]. Whereas interpleural blocks anesthetize multiple intercostal nerves through the diffusion of local anesthetic into the subpleural space, intercostal blocks refer to the injection of local anesthetic directly inferior to the ribs, along the course of the intercostal nerves [161]. A study looking at the use of intercostal nerve blocks for lumpectomy surgery found improved pain relief and decreased opioid consumption [162]. Likewise, intercostal nerve blocks were associated with decreased opioid requirement when used for implant-based breast augmentation [163]. A third study involving breast reconstruction surgery showed a similar decrease in postoperative opioid consumption post [161]. As there is a lack of data evaluating its use in mastectomy studies, further investigation on this topic would be beneficial. Akin to the pectoralis blocks, more data on these techniques need to be collected before recommendations on their use for breast surgeries can be made. Based on early information, it would not be surprising if future research reveals that interpleural and intercostal blocks carry similar risks and benefits to thoracic epidural infusion and paravertebral blockade.

• Chronic postsurgical pain

Pain that lasts for more than 3 months after surgery, otherwise known as chronic postsurgical pain [164], occurs after major breast surgery with an incidence that ranges between 20 and 68% [165–168], depending on differences in definition and the type of breast cancer surgery involved [5].

Patient risk factors for developing chronic postsurgical pain following breast surgery include depression [169], anxiety [170], pain in any anatomic location [171], young age [4,8,167,172–178] and genetics. Intraoperative risk factors include lymph node dissection and axillary staging [8,172,179–181]. Intercostobrachial nerve injury may or may not increase the risk of chronic pain [5]; three retrospective investigations determined it to be associated with higher rates of chronic pain, while four RCTs concluded otherwise [108,182–186]. Postoperative risk factors include increased severity of pain in the immediate postoperative period [4,187–188] and radiation therapy [4,8,108,188–189]. The chance that a postsurgical complication – infection, seroma, hematoma, axillary web syndrome, among others – is associated with chronic pain is low, as only one in four investigations found an association with chronic pain [176,187–188,190].

Paravertebral nerve blocks may decrease chronic pain after major surgical procedures of the breast. Results from one RCT demonstrated that a single-injection paravertebral block with bupivacaine not only decreases pain scores and opioid requirements within the first 24 postoperative hours [17], but decreases the incidence of chronic pain 1, 6 and 12 months after surgery [108]. Three RCTs reported that a 48–72-h continuous paravertebral nerve block infusion decreased pain both during the course of the infusion as well as 2.5, 6 and 12 months following surgery [101,108,191]. A single RCT comparing wound infiltration to single-injection paravertebral nerve blocks did not detect a difference between the two groups at 12 months, and did not report any pain data prior to the 12-month time point [192]. Of note, because the incidence of chronic pain was so low (8%), the study was terminated early as the prospectively defined minimal difference of 20% was determined impossible. Whether the low incidence of pain was due to surgical technique, because both treatments were highly effective in decreasing chronic pain, or due to other factors. 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 postsurgical pain [101,108,191].

The impact of other interventions is less clear. There is a reasonable body of evidence that suggests that decreasing pain acuity in the acute postoperative period will decrease the incidence and severity of chronic postsurgical pain following breast procedures, though the literature is varied. An example of the conflicting evidence can be found in studies involving the perioperative administration of various medications such as mexiletine, venlafaxine, gabapentin, ropivacaine and a eutectic mixture of local anesthetics cream. Although all these interventions have been shown to provide acute postoperative analgesia [51,193–196], it does not always follow that they succeed in reducing the incidence of chronic pain following mastectomy [51,195–196]. The effect of other short term interventions, such as such as the perioperative cutaneous application of an

eutectic mixture of local anesthetic cream [197] and intravenous infusion of lidocaine [198,199], add to the complexity; though both may be unsuccessful in reducing acute postoperative pain in a meaningful way, but they appear to decrease the risk and/or intensity of chronic postsurgical pain.

Conclusion

For patients undergoing major breast surgeries, achieving effective pain control, both acute and chronic, is a major concern. Although research on this topic is abundant, it can be conflicting in nature and challenging to interpret. Nevertheless, a body of data exist to support clinical decisions. The effect of pharmacologic interventions, such as NSAIDS, opioids, antiepileptics, ketamine and lidocaine is controversial, and deserves more investigation. Likewise, data from high-quality randomized, controlled studies on wound infiltration and infusion of local anesthetic (both in standard and liposome encapsulated form) are minimal and conflicting. Conversely, abundant evidence exists on the ability for paravertebral blocks and thoracic epidural infusions to provide effective analgesia and minimize opioid requirement, with a subsequent decrease of opioid-related side effects. Moreover, paravertebral blocks have been associated with decreasing the development of persistent postsurgical pain. Other techniques with promising, but limited data, include brachial plexus blocks, cervical epidural infusion and interfascial plane blocks, interpleural blocks. Further investigation should be done on these procedures and their effect on postoperative pain after breast surgery.

Future perspective

The ideal analgesia following breast cancer surgery will most-likely evolve with additional data on currently available techniques/medications as well as the development of new treatments and analgesic modalities. Further research is needed to guide decisions involving choosing the optimal analgesic for individual patients and surgical procedures; and, optimize the current techniques themselves. Ultrasound guidance will doubtlessly continue to improve, presumably increasing the safety profile of multiple interventional techniques. However, long-acting local anesthetics might allow single-injection blocks to replace perineural local anesthetic infusion; and, possibly increase the effectiveness of simple infiltration.

Financial & competing interests disclosure

The University California San Diego has received research funding for BM Ilfeld's research from Smiths Medical (St Paul, MN, USA), Summit Medical (Sandy, UT, USA), Teleflex Medical (Research Triangle Park, NC, USA), Pacira Pharmaceuticals (Parsippany, NJ, USA), SPR Therapeutics (Chapel Hill, NC, USA) and Myoscience (Redwood City, CA, USA). BM Ilfeld has also received honoraria from Pacira Pharmaceuticals (Parsippany, NJ, USA). These companies had no input into any aspect of manuscript conceptualization or preparation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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