

UC San Diego

UC San Diego Previously Published Works

Title

Persistent Postmastectomy Pain and Pain-Related Physical and Emotional Functioning With and Without a Continuous Paravertebral Nerve Block: A Prospective 1-Year Follow-Up Assessment of a Randomized, Triple-Masked, Placebo-Controlled Study

Permalink

<https://escholarship.org/uc/item/05f3c18w>

Journal

Annals of Surgical Oncology, 22(6)

ISSN

1068-9265

Authors

Ilfeld, Brian M
Madison, Sarah J
Suresh, Preetham J
[et al.](#)

Publication Date

2015-06-01

DOI

10.1245/s10434-014-4248-7

Peer reviewed

Persistent Postmastectomy Pain and Pain-Related Physical and Emotional Functioning With and Without a Continuous Paravertebral Nerve Block: A Prospective 1-Year Follow-Up Assessment of a Randomized, Triple-Masked, Placebo-Controlled Study

Brian M. Ilfeld, Sarah J. Madison, Preetham J. Suresh, NavParkash

Annals of Surgical Oncology

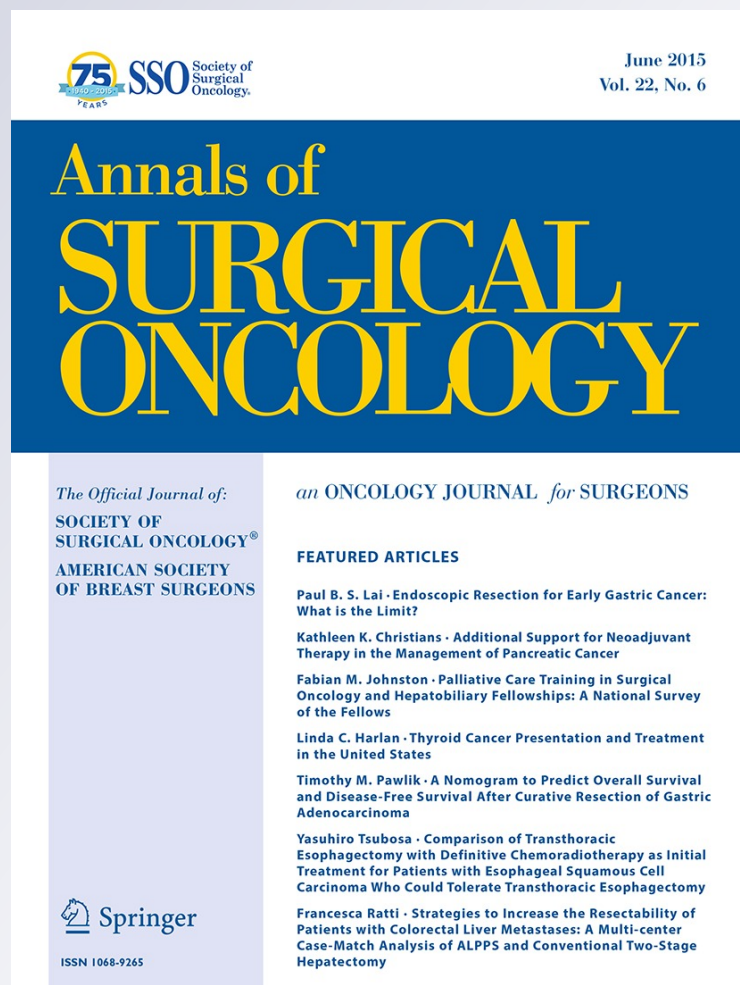
ISSN 1068-9265

Volume 22

Number 6

Ann Surg Oncol (2015) 22:2017-2025

DOI 10.1245/s10434-014-4248-7



Your article is protected by copyright and all rights are held exclusively by Society of Surgical Oncology. This e-offprint is for personal use only and shall not be self-archived in electronic repositories. If you wish to self-archive your article, please use the accepted manuscript version for posting on your own website. You may further deposit the accepted manuscript version in any repository, provided it is only made publicly available 12 months after official publication or later and provided acknowledgement is given to the original source of publication and a link is inserted to the published article on Springer's website. The link must be accompanied by the following text: "The final publication is available at link.springer.com".

Persistent Postmastectomy Pain and Pain-Related Physical and Emotional Functioning With and Without a Continuous Paravertebral Nerve Block: A Prospective 1-Year Follow-Up Assessment of a Randomized, Triple-Masked, Placebo-Controlled Study

Brian M. Ilfeld, MD, MS¹, Sarah J. Madison, MD¹, Preetham J. Suresh, MD¹, NavParkash S. Sandhu, MD, MS¹, Nicholas J. Kormylo, MD¹, Nisha Malhotra, MD¹, Vanessa J. Loland, MD¹, Mark S. Wallace, MD¹, Edward J. Mascha, PhD², Zekun Xu, MS², Cindy H. Wen, BS³, Anya C. Morgan, MA, CCRC¹, and Anne M. Wallace, MD⁴

¹Department of Anesthesiology, University of California San Diego, San Diego, CA; ²Department of Quantitative Health Sciences and Outcomes Research, Cleveland Clinic, Cleveland, OH; ³Department of Ophthalmology, University of California San Diego, San Diego, CA; ⁴Department of Surgery, University of California San Diego, San Diego, CA

ABSTRACT

Background. In a previous randomized, triple-masked, placebo-controlled study, the authors demonstrated that extending a single-injection paravertebral nerve block with a multiple-day perineural local anesthetic infusion improves analgesia and decreases pain-related dysfunction during the 3-day infusion but not subsequent to catheter removal within 1 month after mastectomy. This report describes a prospective follow-up study of the previously published trial to investigate the possibility that extending a single-injection paravertebral block with a multiple-day infusion may decrease persistent postsurgical pain as well as pain-induced emotional and functional dysfunction 1 year after mastectomy.

Methods. Subjects undergoing uni- or bilateral mastectomy received unilateral ($n = 24$) or bilateral ($n = 36$) single-injection thoracic paravertebral block(s) with ropivacaine and perineural catheter(s). The subjects were randomized to receive either ropivacaine 0.4 % ($n = 30$)

or normal saline ($n = 30$) via their catheters until the catheters were removed on postoperative day 3. Chronic pain and pain-related physical and emotional dysfunction were measured using the Brief Pain Inventory (BPI).

Results. No statistically significant difference between treatments 3 months after surgery was observed with the BPI. In contrast, after 12 months, only 4 subjects (13 %) who had received a perineural ropivacaine infusion reported pain-induced dysfunction compared with 14 (47 %) who had received saline infusion ($P = 0.011$). At 12 months, the mean BPI was 1.6 ± 4.6 for the subjects who received ropivacaine versus 5.9 ± 11.3 for the subjects who received saline ($P = 0.007$).

Conclusions. Adding a multiple-day, continuous ropivacaine infusion to a single-injection ropivacaine paravertebral nerve block may result in a lower incidence of pain as well as pain-related physical and emotional dysfunction 1 year after mastectomy.

Presented in part as a scientific abstract at the annual meeting of the American Society of Anesthesiologists in New Orleans, LA, 13 October 2014.

© Society of Surgical Oncology 2014

First Received: 7 September 2014;

Published Online: 21 November 2014

B. M. Ilfeld, MD, MS

e-mail: bilfeld@ucsd.edu

After mastectomy, pain during the acute postoperative period is frequently moderate or severe¹ and closely associated with subsequent persistent postsurgical pain lasting months² or even years.^{3,4} Such chronic pain has an incidence of 30–73 %, ^{4–6} and is strongly correlated with depression and anxiety.⁷ There is evidence that intense analgesia immediately after surgery may decrease the incidence or severity of chronic pain.^{8,9} Potent analgesia can be provided with a paravertebral nerve block in which local anesthetic is

percutaneously injected adjacent to the peripheral nerves innervating the breast.^{1,9} Although single-injection paravertebral nerve blocks have a duration of only 8–24 h,¹⁰ they have been associated with a lower incidence of chronic pain 4–12 months after mastectomy.^{9,11,12}

In laboratory animals, prolonging a neural blockade multiple days can further reduce the development of neuropathic pain.¹³ In humans, single-injection peripheral nerve blocks in nearly any anatomic location may be extended indefinitely with the insertion of a perineural catheter and subsequent continuous local anesthetic infusion.¹⁴ Using a portable infusion pump, protracted-duration analgesia may be provided in the comfort of patients' own homes.¹⁵ For example, our group recently reported that extending a single-injection ropivacaine paravertebral block with a multiple-day, ambulatory perineural ropivacaine infusion decreased pain as well as pain-induced physical and emotional dysfunction during the infusion.¹⁶ However, it remains unknown whether extended paravertebral blocks result in a decreased incidence of persistent postsurgical pain in the ipsilateral breast, axilla, and arm 1 year after mastectomy.

Furthermore, although the prevalence of postmastectomy phantom breast pain—painful sensations perceived in the breast that is no longer present¹⁷—varies greatly, it is reported to be as high as 44%.⁵ There is prospective clinical evidence that after upper and lower extremity amputation, continuous brachial plexus, sciatic, and femoral nerve blocks may decrease the incidence or severity of phantom limb pain.^{18,19}

Whether a continuous paravertebral block reduces phantom breast pain remains uninvestigated. Consequently, we designed and executed this prospective follow-up study of our previously published randomized, triple-masked, placebo-controlled clinical trial involving short-term outcomes¹⁶ to determine whether extending a single-injection paravertebral block with a multiple-day infusion decreases chronic breast pain as well as pain-induced emotional and functional dysfunction 1 year after mastectomy.

METHODS

Enrollment

The trial was prospectively registered at clinicaltrials.gov (NCT01231204). The protocol was in accordance with the precepts established by the World Medical Association's Helsinki Declaration of 1964 and subsequent amendments.²⁰ The local Institutional Review Board (University of California San Diego, San Diego, CA, USA) approved all study procedures, and all study subjects provided written informed consent.

Details of the study methods have been published previously.¹⁶ In brief, enrollment was offered to women 18 years of age or older undergoing uni- or bilateral mastectomy with or without axillary lymph node dissection and desiring a single-injection paravertebral nerve block(s) for postoperative analgesia.

Preoperatively, all the subjects received an ipsilateral paravertebral perineural catheter inserted with ultrasound guidance between the third and fourth thoracic vertebrae (StimuCath Plus, Teleflex Medical, Research Triangle Park, NC, USA) followed by a single injection of long-acting local anesthetic (15 mL of ropivacaine 0.5 %, with epinephrine 5 µg/mL). For the subjects undergoing bilateral mastectomy, a catheter using the same protocol was subsequently inserted in the contralateral side. Intraoperatively, the subjects received a general anesthetic, with induction using intravenous propofol and maintenance using inhaled volatile anesthetic combined with nitrous oxide. An intravenous opioid (fentanyl, hydromorphone, or morphine) was titrated to heart rate and blood pressure increases as needed. All subjects underwent immediate reconstruction after mastectomy and had two drains inserted per mastectomy.

Study Intervention

Before the subject left the operating room, a perineural infusion was initiated using an elastomeric portable infusion pump with a fixed rate of 5 mL/h and a 300-mL reservoir (LV5 Infusor, Baxter Healthcare International, Deerfield, IL, USA). Investigational pharmacists randomized the subjects to one of two treatment groups: the placebo group (normal saline) or the ropivacaine group (0.4 %). The subjects undergoing a bilateral mastectomy received two separate infusion pumps, each affixed to a separate catheter and always containing the identical solution. Subjects, investigators, observers, statisticians, and all clinical staff were masked to treatment group assignment through data analysis. The subjects remained hospitalized at least one night and were subsequently discharged home with their perineural catheter or catheters in situ, which were removed on postoperative day (POD) 3. The subjects remained masked to treatment group for the entire 12-month duration of their participation.

Postoperative Analgesics

For postoperative analgesia during the immediate postoperative period, all the subjects received the single-injection ropivacaine paravertebral block (initiated via the catheter) as well as oral acetaminophen (975 mg four times daily). Administration of rescue analgesics for breakthrough pain was determined by pain severity using the following numeric rating scale (NRS): oxycodone 5 mg

(NRS < 4) or 10 mg (NRS \geq 4). This protocol was used both before and after discharge. During the patient's hospital stay, pain was reassessed 30 min later, and intravenous morphine (2–4 mg) was repeated every 30 min until the NRS was lower than 4.

Outcome Measurements (End Points)

Data were collected by telephone on PODs 1, 4, 8, and 28 and then at months 3 and 12. The Brief Pain Inventory (short form) is an instrument specifically designed to assess pain and its impact on physical and emotional functioning within the previous 24 h.^{21,22} It has established reliability and validity, with minimal interrater discordance, and is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement.²³ The Brief Pain Inventory consists of three domains: (1) *pain*, with four questions involving “worst,” “average,” “least,” and “current” pain levels using an NRS with a range of 0 (no pain) to 10 (worst pain imaginable), (2) percentage of *relief* provided by pain treatments, with one question and a reported score calculated as the percentage divided by 10 then subtracted from 10 and ranging from 0 (complete relief) to 10 (no relief), and, (3) *interference*, with seven questions involving physical and emotional functioning using a Likert scale with a range of 0 (no interference) to 10 (complete interference). The use of both single items (e.g., average pain) and a composite score ranging from 0 (optimal) to 120 (worst possible) is supported by the IMMPACT recommendations for assessing pain in clinical trials.^{24–26}

Additional information was gathered including the incidence and intensity (measured on the NRS) of phantom breast pain, defined as painful sensations perceived in breast tissue after surgical resection¹⁷; difficulty sleeping because of pain (binary variable: yes or no); and the number of awakenings perceived due to pain.

Statistical Analysis

For the follow-up study of the chronic pain phase, the primary outcome was defined as the total Brief Pain Inventory score at 12 months. We assessed the effect of ropivacaine (vs placebo) on this ordinal outcome using the Mann–Whitney *U* test at the 0.05 significance level.²⁷ Binary outcomes between treatments were compared with the Pearson Chi square test. No adjustment was made for multiple comparisons, and statistically significant findings in secondary outcomes should be viewed as suggestive, requiring confirmation in a future trial before they are considered definitive.

The study was powered for the previously published acute-phase primary end point: the difference between the two treatment groups in average NRS queried the day after

surgery.¹⁶ With a total of 60 subjects and assuming a standard deviation of 11.3 for the primary outcome (based on unpublished data), we had more than 80 % power to detect a mean difference of 8.3 or greater at the 0.05 significance level.

Very few data points were missing at 3 and 12 months. For the primary outcome, missing data were imputed for two ropivacaine patients and one placebo patient. For missing outcome data, we used the “worst case” scenario as the primary analysis (i.e., assigning the worst observed value to missing data for ropivacaine patients and the best observed value for placebo patients). In sensitivity analyses, we used the best case scenario (assigning the best observed value for ropivacaine and the worst observed value for placebo) and the last observation-carried-forward method. All statistical analyses were performed with R software version 2.15.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During a 24-month period beginning December 2010, 60 subjects had unilateral ($n = 24$) or bilateral ($n = 36$) catheter(s) inserted successfully per protocol (Table 1). No seroma formations or wound/catheter infections occurred.

Acute Phase

The results for the acute phase of the postoperative period have been published previously.¹⁶ In brief, the average pain queried on POD 1 for the subjects receiving perineural ropivacaine ($n = 30$) was a median (interquartile range) of 2 (IQR 0–3) compared with 4 (IQR 1–5) for the subjects receiving saline ($n = 30$; $P = 0.021$). As a result, during the infusion on POD 1, the subjects receiving perineural ropivacaine experienced less pain-induced physical and emotional dysfunction, as measured with the Brief Pain Inventory (lower score = less dysfunction): 14 (IQR 4–37) versus 57 (IQR 8–67) for the subjects receiving perineural saline ($P = 0.012$). In contrast, after discontinuation of infusion, no statistically significant differences were detected between the treatment groups on PODs 4, 8, and 28.

Follow-Up Study

No statistically significant difference between treatments was observed 3 months after surgery (Table 2): the mean Brief Pain Inventory was 14.1 ± 28.6 for the subjects receiving ropivacaine versus 6.2 ± 11.7 for the subjects receiving saline ($P = 0.624$). Nine months later—12 months after surgery (Table 3)—the mean Brief Pain Inventory for the subjects who received ropivacaine had decreased to 1.6 ± 4.6 . In contrast, during this same period, the mean Brief Pain Inventory for the subjects who

TABLE 1 Population data and procedural information

Perineural infusion	Ropivacaine (n = 30)	Placebo (n = 30)
Age (years)	48 (40–54)	49 (40–57)
Height (cm)	165 (161–170)	166 (163–170)
Weight (kg)	62 (56–72)	61 (54–69)
Body mass index (kg/m ²)	23 (20–26)	24 (20–26)
Unilateral mastectomy		
With lymph node dissection	8	10
Without lymph node dissection	3	3
Bilateral mastectomy		
With lymph node dissection	14	12
Without lymph node dissection	5	5
Surgical duration (min)	190 (125–205)	184 (132–229)
Worst pain during catheter insertion (NRS)	5.0 (2.5–6.0)	2.5 (1.3–4.5)
Midazolam for catheter insertion(s) (mg)	2 (2–3)	2 (2–4)
Fentanyl for catheter insertion(s) (μg)	100 (50–100)	100 (75–100)

Values are reported as median (interquartile range) or as number of subjects as indicated

NRS numeric rating scale

received saline changed minimally (5.9 ± 11.3) (intergroup comparison: $P = 0.007$). A similar pattern was found in the total of subjects experiencing any pain. At 3 months, 10 subjects (33 %) who had received ropivacaine reported pain versus 13 subjects (43 %) who had received placebo ($P = 0.595$). In contrast, by 12 months postoperatively, the number of subjects in the ropivacaine group experiencing any pain had dropped to 4 (13 %) versus an increase to 14 subjects (47 %) in the placebo group (Table 4; $P = 0.011$).

Phantom Pain

At month 3, five subjects (17 %) who had received ropivacaine reported phantom breast pain (Table 2), whereas one subject (3 %) who had received placebo reported this type of pain ($P = 0.085$). However, by month 12, only one subject (3 %) in the ropivacaine group experienced any phantom pain (described as occurring only a single time in the previous 9 months) compared with nine subjects (30 %) in the placebo group ($P = 0.006$).

DISCUSSION

This prospective follow-up study of a randomized, triple-masked, placebo-controlled clinical trial suggests that adding

a multiple-day, continuous ropivacaine infusion to a single-injection paravertebral nerve block during the immediate postoperative period results in a lower incidence of pain and pain-related physical and emotional dysfunction 1 year after mastectomy. These results have broad clinical implications considering the tens of thousands of patients undergoing mastectomy in the United States alone,^{28,29} who have a relatively high risk for the development of chronic pain.⁵

Acute Versus Chronic Pain

Our finding that a prolonged paravertebral nerve block decreases pain and pain-related dysfunction during the infusion and 1 year after mastectomy—but not during the intervening period—may seem implausible. However, it actually conforms to the current consensus that acute and chronic pain states have related but differing etiologies.² Pain in the immediate postoperative period is induced by tissue injury resulting in nociceptive input from afferent nerves as well as reversible peripheral and central sensitization that results in primary and secondary hyperalgesia.² Inflammatory mediators released from injured tissue play a central role and may greatly magnify sensitization (and therefore pain response). By medically truncating afferent nerves, peripheral nerve blocks are potent inhibitors of nociceptive input,³⁰ and as a result, continuous peripheral nerve blocks provide intense prolonged analgesia during the local anesthetic infusion.¹⁴ Our previously published results reflect this for postmastectomy patients by the finding that analgesia-related benefits afforded patients a continuous paravertebral nerve block during the ropivacaine infusion.¹⁶

Unfortunately, with few exceptions, little evidence exists that patients experience analgesic benefits of continuous peripheral nerve blocks after cessation of the local anesthetic infusion.¹⁴ This finding suggests that continuous peripheral nerve blocks have minimal lasting effect on the causes of acute pain such as inflammatory responses and consequential reversible peripheral sensitization, local neural hyperexcitability, and hyperalgesia.² The results of our study conform to this theory because no statistically significant differences between treatments were observed from catheter removal through 3 months after surgery.¹⁶

Additionally, the reversible nature of sensitization is reflected in our study. Of the subjects who experienced pain at 3 months, 7 of 10 subjects (70 %) who received ropivacaine and 3 of 13 subjects (23 %) who received placebo had complete resolution of pain by month 12 (intergroup comparison: $P = 0.024$).

Persistent Postsurgical Pain

Although the etiology of chronic pain is multifactorial and not completely understood, the pathogenic

TABLE 2 Comparison of ropivacaine and placebo paravertebral perineural infusion in terms of pain and its impact on physical and emotional functioning 3 months after mastectomy

	Mean \pm SD		Median (IQR)		P value
	Ropivacaine (n = 30)	Placebo (n = 30)	Ropivacaine (n = 30)	Placebo (n = 30)	
Pain in the last 24 h (0–10)					
Worst	1.4 \pm 2.5	1.7 \pm 2.4	0 (0–1)	0 (0–3)	0.422
Average	0.5 \pm 0.3	0.4 \pm 1.0	0 (0–0)	0 (0–0)	0.955
Least	0.1 \pm 0.3	0.1 \pm 0.4	0 (0–0)	0 (0–0)	0.861
Current	0.4 \pm 1.1	0.3 \pm 0.7	0 (0–0)	0 (0–0)	0.920
Pain subscale total (0–40)	2.1 \pm 4.4	2.5 \pm 3.9	0 (0–1)	0 (0–4)	0.317
Relief from treatments (0–10) ^a	9.1 \pm 1.9	9.1 \pm 2.2	10 (10–10)	10 (10–10)	0.838
Interference with (0–10; 0 = none)					
General activity	0.9 \pm 2.4	0.7 \pm 1.8	0 (0–0)	0 (0–0)	0.844
Mood	1.2 \pm 3.1	0.4 \pm 1.3	0 (0–0)	0 (0–0)	0.829
Walking	0.4 \pm 1.3	0.1 \pm 0.4	0 (0–0)	0 (0–0)	0.622
Work (inside/outside home)	1.1 \pm 2.9	0.5 \pm 1.3	0 (0–0)	0 (0–0)	0.927
Relationships	1.0 \pm 2.6	0.2 \pm 0.6	0 (0–0)	0 (0–0)	0.208
Sleep	0.6 \pm 1.9	0.5 \pm 1.7	0 (0–0)	0 (0–0)	0.977
Enjoyment of life	1.1 \pm 2.8	0.4 \pm 1.3	0 (0–0)	0 (0–0)	0.617
Interference subscale total (0–70)	6.3 \pm 16.3	2.9 \pm 7.2	0 (0–0)	0 (0–0)	0.939
Brief Pain Inventory total 0–120 ^a	14.1 \pm 28.6	6.2 \pm 11.7	0 (0–2)	0 (0–6)	0.624
Brief Pain Inventory total >0: n (%) ^a	10 (33)	13 (43)	10 (33)	13 (43)	0.595
Phantom pain					
Worst (0–10)	1.2 \pm 2.3	0.1 \pm 0.5	0 (0–0)	0 (0–0)	0.021
Average (0–10)	0.5 \pm 1.1	0.0 \pm 0.2	0 (0–0)	0 (0–0)	0.041
Incidence (average times per day)	0.8 \pm 2.3	0.0 \pm 0.0	0 (0–0)	0 (0–0)	0.006
Due to surgical pain					
Awakenings (occurrences)	0.1 \pm 0.3	0.2 \pm 0.7	0 (0–0)	0 (0–0)	0.611
Difficulty sleeping: n (%)	0 (0)	2 (7)	0 (0)	2 (7)	0.472

Unless noted otherwise, for all variables, one missing value in the ropivacaine group and one missing value in the placebo group were imputed. Missing data were imputed assuming the worst observed outcome for ropivacaine and the best observed outcome for placebo

SD standard deviation, IQR interquartile range

^a Missing values in the ropivacaine (n = 4) and placebo (n = 2) groups were imputed

mechanisms differ somewhat from those of acute pain.³¹ In contrast to the inflammation-induced plasticity of the acute phase, the perioperative barrage of nociceptive input triggered by direct tissue injury provokes changes in the central nervous system that may result in chronic pain.^{2,32,33} In addition, injury to peripheral nerves results in reorganization in the peripheral and central nervous systems, resulting in chronic pain. This reorganization occurs over many weeks and months and may result in persistent abnormalities in sensory processing, resulting in persistent pain.^{34–37}

Our study found improved pain control during the first days in the continuous local anesthetic infusion group, suggesting that short-term reductions in postsurgical pain can significantly dampen the long-term persistent changes in nervous system function that occur with nerve injury. Although the International Association for the Study of Pain

defines persistent postsurgical pain as occurring after more than 2 months, the duration of the acute pain phase varies greatly by surgical procedure.³¹ For breast surgery, the division between acute and chronic periods is considered at some point between 3 and 6 months.^{5,38} The results from our study reflected this. No statistically significant differences between treatments were observed at 3 months, and five subjects who had not experienced pain at 3 months had chronic pain by month 12 (1 from the group that had received perineural ropivacaine and 4 from the placebo group; Table 4).

Because continuous peripheral nerve blocks greatly decrease nociceptive input over the course of multiple postoperatively days, they may preempt the signals resulting in the central nervous system “windup” that contribute to chronic pain.¹³ Regarding mastectomy, intense perioperative pain is associated with an increased risk of chronic pain,⁷ and providing potent perioperative

TABLE 3 Comparison of ropivacaine and placebo paravertebral perineural infusion in terms of pain and its impact on physical and emotional functioning 12 months after mastectomy

	Mean \pm SD		Median (IQR)		<i>P</i> value
	Ropivacaine (<i>n</i> = 30) ^a	Placebo (<i>n</i> = 30) ^a	Ropivacaine (<i>n</i> = 30) ^a	Placebo (<i>n</i> = 30) ^a	
Pain in the last 24 h (0–10)					
Worst	0.5 \pm 1.5	1.5 \pm 2.0	0 (0–0)	0 (0–3)	0.005
Average	0.3 \pm 0.9	0.2 \pm 0.5	0 (0–0)	0 (0–0)	0.582
Least	0.2 \pm 0.6	0.1 \pm 0.3	0 (0–0)	0 (0–0)	0.356
Current	0.2 \pm 0.6	0.3 \pm 0.7	0 (0–0)	0 (0–0)	0.700
Pain subscale total (0–40)	1.2 \pm 3.7	2.0 \pm 2.9	0 (0–0)	0 (0–3)	0.015
Relief from treatments (0–10)	9.9 \pm 0.3	9.3 \pm 1.7	10 (10–10)	10 (9–10)	0.082
Interference with (0–10; 0 = none)					
General activity	0.1 \pm 0.3	0.6 \pm 1.4	0 (0–0)	0 (0–0)	0.354
Mood	0.0 \pm 0.0	0.6 \pm 1.5	0 (0–0)	0 (0–0)	0.022
Walking	0.0 \pm 0.0	0.0 \pm 0.2	0 (0–0)	0 (0–0)	0.334
Work (inside/outside home)	0.0 \pm 0.0	0.3 \pm 0.8	0 (0–0)	0 (0–0)	0.042
Relationships	0.0 \pm 0.0	0.4 \pm 1.4	0 (0–0)	0 (0–0)	0.082
Sleep	0.0 \pm 0.0	0.7 \pm 1.9	0 (0–0)	0 (0–0)	0.354
Enjoyment of life	0.1 \pm 0.3	0.6 \pm 1.4	0 (0–0)	0 (0–0)	0.216
Interference subscale total (0–70)	0.2 \pm 0.6	3.2 \pm 7.9	0 (0–0)	0 (0–0)	0.381
Brief Pain Inventory total (0–120)	1.6 \pm 4.6	5.9 \pm 11.3	0 (0–0)	0 (0–6)	0.007
Brief Pain Inventory total >0: <i>n</i> (%)	4 (13)	14 (47)	4 (13)	14 (47)	0.082
Phantom pain					
Worst (0–10)	0.3 \pm 0.8	0.7 \pm 1.4	0 (0–0)	0 (0–1)	0.083
Average (0–10)	0.0 \pm 0.0	0.5 \pm 1.1	0 (0–0)	0 (0–0)	0.006
Incidence (average times/day)	0.0 \pm 0.0	0.7 \pm 1.8	0 (0–0)	0 (0–1)	0.029
Due to surgical pain					
Awakenings (occurrences)	0.0 \pm 0.0	0.1 \pm 0.4	0 (0–0)	0 (0–2)	0.082
Difficulty sleeping: <i>n</i> (%)	0 (0)	5 (17)	0 (0)	5 (17)	0.062

SD standard deviation, *IQR* interquartile range

^a Data were imputed for two patients with missing values in the ropivacaine group and for one patient in the placebo group. Missing data were imputed assuming the worst observed outcome for ropivacaine and the best observed outcome for placebo

analgesia with a single-injection paravertebral nerve block is correlated with a lower incidence of chronic pain 4–12 months postoperatively.^{11,12}

Our study suggests that using a perineural local anesthetic infusion to prolong the potent analgesia afforded by a single-injection block decreases the risk for the development of chronic pain ($P = 0.007$), including phantom breast pain (incidence of 3 % at 12 months for the ropivacaine group and 30 % for the placebo group; $P = 0.006$).

In summary, pain during the first 3–6 months after mastectomy often is induced or worsened by factors that continuous peripheral nerve blocks affect only marginally (e.g., inflammatory mediator release).^{39,40} In contrast, persistent postoperative pain often results from nociceptive communication from injured peripheral tissue to the central nervous system via afferent nerves in the immediate postoperative period, and it is this communication that peripheral nerve blocks dramatically attenuate.³⁰

Interestingly, a recently published randomized trial by Karmakar et al.⁴¹ with a protocol very similar to that of the current study reported a similar decrease in the incidence and intensity of chronic pain 6 months after mastectomy, but only for subjects who received both a single-injection paravertebral block and subsequent 72-h perineural infusion compared with no regional anesthetic/analgesic. However, no statistically significant difference was detected between the subjects with a single-injection paravertebral block and perineural local anesthetic infusion and those who received a single-injection block and placebo infusion (essentially the treatment groups of the current study). We can only speculate on the origin of the difference in findings between the previous and current studies, but it is possible that the use of ropivacaine 0.25 versus 0.4 % of the current study (at approximately the same basal rates of 5–6 mL/h), which induces a greater insensate surgical area, was responsible for the contrasting results.¹⁸

TABLE 4 Comparison of ropivacaine and placebo paravertebral perineural infusion in terms of pain and its impact on physical and emotional functioning 3 and 12 months after mastectomy

BPI: Brief Pain Inventory	Ropivacaine (n = 30) n (%)	Placebo (n = 30) n (%)	P Value
Subjects with BPI > 0 at 3 months ^a	10	13	0.595
Subjects with BPI > 0 at 3 months for whom at 12 months			
Pain resolved (BPI = 0) ^b	7 (70)	3 (23)	0.024
Pain continued (BPI > 0) ^b	3 (30)	10 (77)	
Subjects with no pain at 3 months but development of pain by 12 months ^b	1	4	0.100
Subjects with BPI > 0 at 12 months ^b	4	14	0.011

Missing data were imputed assuming the worst observed outcome for ropivacaine and the best observed outcome for placebo. Data are presented as number of subjects (%)

BPI Brief Pain Inventory

^a Data were imputed for four patients with missing values in the ropivacaine group and for two patients in the placebo group

^b Data were imputed for two patients with missing values in the ropivacaine group and for one patient in the placebo group

Study Limitations

This investigation had several limitations. First, our study was powered for the primary end point involving pain during the perineural infusion, and although the current analysis was performed prospectively, the findings for the secondary outcomes should be viewed as suggestive, requiring confirmation in a subsequent trial. Second, we provided a basal infusion of 5 mL/h (ropivacaine 0.4 %, or 20 mg/h) exclusively without patient-controlled bolus doses. The optimal delivery regimen for paravertebral infusions remains unknown, so a higher basal infusion rate (>5 mL/h) or local anesthetic concentration (>0.4 %) than used in this study may yield superior results. Relatedly, nonsteroidal antiinflammatory agents, gabapentin, and local anesthetic wound infiltration/infusion were not used per the surgeon's preferred standard analgesic regimen, the addition of which may have decreased the differences found between the two treatment groups.^{42–44} In addition, although the overwhelming number of investigations, including those of the current study, involving breast surgery and paravertebral infusion included the third thoracic level for catheter insertion,^{45–52} the optimal level for mastectomy analgesia remains unknown. We did not measure blood levels of nociceptive processing or stress response markers that could have helped elucidate any association of perioperative analgesia with persistent postoperative pain and cancer recurrence.^{50,53}

A large body of evidence exists on the role of conditioned pain modulation (CPM) in the development of chronic pain, including postsurgery chronic pain syndromes.⁵⁴ The thought that less efficient CPM increases the risk for the development of chronic pain after surgery has been substantiated. Patients with less efficient CPM (determined preoperatively) undergoing thoracotomy and abdominal surgery have shown a significantly higher incidence of chronic pain.^{55,56}

We did not test for CPM, and this may account for the differences. Similarly, we did not perform a baseline psychosocial assessment. Differences in psychosocial status (i.e., stress, anxiety, depression, work status) between groups can account for differences in chronic pain incidence.

Finally, we did not collect data on patient comorbidities, postoperative adjuvant therapy, cancer recurrence, or chronic pain medications. However, with a randomized study design and a total of 60 subjects, it is probable that such variables were relatively evenly distributed between the two treatment groups, and it is highly improbable that small random differences in such variables would account for the large treatment effect (4 [13 %] vs 14 [47 %] with chronic pain) we found 12 months postoperatively.

In summary, this investigation suggests that adding a multiple-day, ambulatory, continuous ropivacaine infusion to a single-injection ropivacaine paravertebral nerve block may result in less chronic pain and functional deficit 1 year after mastectomy.

ACKNOWLEDGMENT Funding for this project was provided by National Institutes of Health Grant GM077026 (P.I.: Dr. Ilfeld) from the National Institute of General Medical Sciences (Bethesda, MD, USA); the Clinical and Translational Research Institute, University of California, San Diego (San Diego, CA, USA), with funding provided by National Institutes of Health grants UL1RR031980 and UL1TR000100; the Department of Anesthesiology, University of California San Diego (San Diego, CA, USA) and Baxter Healthcare International (Deerfield, IL, USA). This company also provided the portable infusion pumps used in the original investigation but had no input into any aspect of study conceptualization, design and implementation, data collection, analysis and interpretation, or manuscript preparation. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the funding entities.

DISCLOSURE There are no conflicts of interest.

REFERENCES

1. Kairaluoma PM, Bachmann MS, Korpinen AK, Rosenberg PH, Pere PJ. Single-injection paravertebral block before general anesthesia enhances analgesia after breast cancer surgery with and without associated lymph node biopsy. *Anesth Analg*. 2004;99:1837–43.

2. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367:1618–25.
3. Gartner R, Jensen MB, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA*. 2009;302:1985–92.
4. Mejdahl MK, Andersen KG, Gartner R, Kroman N, Kehlet H. Persistent pain and sensory disturbances after treatment for breast cancer: six-year nationwide follow-up study. *BMJ*. 2013;346:1865.
5. Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: proposed classification and research update. *Pain*. 2003;104:1–13.
6. Tasmuth T, von Smitten K, Hietanen P, Kataja M, Kalso E. Pain and other symptoms after different treatment modalities of breast cancer. *Ann Oncol*. 1995;6:453–9.
7. Tasmuth T, Estlander AM, Kalso E. Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. *Pain*. 1996;68:343–7.
8. Senturk M, Ozcan PE, Talu GK, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg*. 2002;94:11–5.
9. Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. *Br J Anaesth*. 2013;111:711–20.
10. Klein SM, Bergh A, Steele SM, Georgiade GS, Greengrass RA. Thoracic paravertebral block for breast surgery. *Anesth Analg*. 2000;90:1402–5.
11. Kairaluoma PM, Bachmann MS, Rosenberg PH, Pere PJ. Preincisional paravertebral block reduces the prevalence of chronic pain after breast surgery. *Anesth Analg*. 2006;103:703–8.
12. Ibarra MM, S-Carralero GC, Vicente GU, Cuartero del Pozo A, Lopez Rincon R, Fajardo del Castillo MJ. Chronic postoperative pain after general anesthesia with or without a single-dose preincisional paravertebral nerve block in radical breast cancer surgery (in Spanish). *Rev Espanola Anestesiol Reanimacion*. 2011;58:290–4.
13. Shankarappa SA, Tsui JH, Kim KN, et al. Prolonged nerve blockade delays the onset of neuropathic pain. *Proc Nat Acad Sci USA*. 2012;109:17555–60.
14. Ilfeld BM. Continuous peripheral nerve blocks: a review of the published evidence. *Anesth Analg*. 2011;113:904–25.
15. Ilfeld BM, Enneking FK. Continuous peripheral nerve blocks at home: a review. *Anesth Analg*. 2005;100:1822–33.
16. Ilfeld BM, Madison SJ, Suresh PJ, et al. Treatment of postmastectomy pain with ambulatory continuous paravertebral nerve blocks: a randomized, triple-masked, placebo-controlled study. *Reg Anesth Pain Med*. 2014;39:89–96.
17. Dijkstra PU, Rietman JS, Geertzen JH. Phantom breast sensations and phantom breast pain: a 2-year prospective study and a methodological analysis of literature. *Eur J Pain*. 2007;11:99–108.
18. Borghi B, D'Addabbo M, White PF, et al. The use of prolonged peripheral neural blockade after lower extremity amputation: the effect on symptoms associated with phantom limb syndrome. *Anesth Analg*. 2010;111:1308–15.
19. Ilfeld BM, Moeller-Bertram T, Hanling SR, et al. Treating intractable phantom limb pain with ambulatory continuous peripheral nerve blocks: a pilot study. *Pain Med*. 2013;14:935–42.
20. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *JAMA*. 2000;284:3043–5.
21. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*. 1994;23:129–38.
22. Mendoza TR, Chen C, Brugger A, et al. The utility and validity of the modified brief pain inventory in a multiple-dose postoperative analgesic trial. *Clin J Pain*. 2004;20:357–62.
23. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2010;149:177–93.
24. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9–19.
25. Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2009;146:238–44.
26. Turk DC, Dworkin RH, Burke LB, et al. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. *Pain*. 2006;125:208–15.
27. Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. *Ann Math Stat*. 1947;18:50–60.
28. Howlander N, Noone AM, Krapcho M, et al (2014) *SEER Cancer Statistics Review, 1975–2009*. National Cancer Institute: Bethesda.
29. Habermann EB, Abbott A, Parsons HM, Virnig BA, Al-Refai WB, Tuttle TM. Are mastectomy rates really increasing in the United States? *J Clin Oncol*. 2010;28:3437–41.
30. Birbaumer N, Lutzenberger W, Montoya P, et al. Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. *J Neurosci*. 1997;17:5503–8.
31. Kehlet H, Rathmell JP. Persistent postsurgical pain: the path forward through better design of clinical studies. *Anesthesiology*. 2010;112:514–5.
32. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:1959–64.
33. Nikolajsen L, Ilkjaer S, Jensen TS. Relationship between mechanical sensitivity and postamputation pain: a prospective study. *Eur J Pain*. 2000;4:327–34.
34. Devor M, Govrin-Lippmann R, Angelides K. Na⁺ channel immunolocalization in peripheral mammalian axons and changes following nerve injury and neuroma formation. *J Neurosci*. 1993;13:1976–92.
35. McLachlan EM, Janig W, Devor M, Michaelis M. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. *Nature*. 1993;363:543–6.
36. Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature*. 1992;355:75–8.
37. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. *Science*. 2000;288:1765–9.
38. Kwekkeboom K. Postmastectomy pain syndromes. *Cancer Nurs*. 1996;19:37–43.
39. Bagry H, de la Cuadra Fontaine JC, Asenjo JF, Bracco D, Carli F. Effect of a continuous peripheral nerve block on the inflammatory response in knee arthroplasty. *Reg Anesth Pain Med*. 2008;33:17–23.
40. Martin F, Martinez V, Mazoit JX, et al. Antiinflammatory effect of peripheral nerve blocks after knee surgery: clinical and biologic evaluation. *Anesthesiology*. 2008;109:484–90.
41. Karmakar MK, Samy W, Li JW, et al. Thoracic paravertebral block and its effects on chronic pain and health-related quality of life after modified radical mastectomy. *Reg Anesth Pain Med*. 2014;39:289–98.
42. Vallejo MC, Phelps AL, Sah N, et al. Preemptive analgesia with bupivacaine for segmental mastectomy. *Reg Anesth Pain Med*. 2006;31:227–32.
43. Sidiropoulou T, Buonomo O, Fabbi E, et al. A prospective comparison of continuous wound infiltration with ropivacaine versus single-injection paravertebral block after modified radical mastectomy. *Anesth Analg*. 2008;106:997–1001.
44. Albi-Feldzer A, Mouret-Fourme EE, Hamouda S, et al. A double-blind randomized trial of wound and intercostal space infiltration

- with ropivacaine during breast cancer surgery: effects on chronic postoperative pain. *Anesthesiology*. 2013;118:318–26.
45. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology*. 2006;105:660–4.
 46. McElwain J, Freir NM, Burlacu CL, Moriarty DC, Sessler DI, Buggy DJ. The feasibility of patient-controlled paravertebral analgesia for major breast cancer surgery: a prospective, randomized, double-blind comparison of two regimens. *Anesth Analg*. 2008;107:665–8.
 47. Buckenmaier CC, III, Klein SM, Nielsen KC, Steele SM. Continuous paravertebral catheter and outpatient infusion for breast surgery. *Anesth Analg*. 2003;97:715–7.
 48. Buckenmaier CC III, Kwon KH, Howard RS, et al. Double-blinded, placebo-controlled, prospective randomized trial evaluating the efficacy of paravertebral block with and without continuous paravertebral block analgesia in outpatient breast cancer surgery. *Pain Med*. 2010;11:790–9.
 49. Burlacu CL, Frizelle HP, Moriarty DC, Buggy DJ. Fentanyl and clonidine as adjunctive analgesics with levobupivacaine in paravertebral analgesia for breast surgery. *Anaesthesia*. 2006;61:932–7.
 50. Iohom G, Abdalla H, O'Brien J, et al. The associations between severity of early postoperative pain, chronic postsurgical pain, and plasma concentration of stable nitric oxide products after breast surgery. *Anesth Analg*. 2006;103:995–1000.
 51. Buggy DJ, Kerin MJ. Paravertebral analgesia with levobupivacaine increases postoperative flap tissue oxygen tension after immediate latissimus dorsi breast reconstruction compared with intravenous opioid analgesia. *Anesthesiology*. 2004;100:375–80.
 52. Schnabel A, Reichl SU, Kranke P, Pogatzki-Zahn EM, Zahn PK. Efficacy and safety of paravertebral blocks in breast surgery: a meta-analysis of randomized controlled trials. *Br J Anaesth*. 2010;105:842–52.
 53. Naesh O, Haljamae H, Hindberg I, Holm J, Jivegard L, Wennmalm A. Epidural anaesthesia prolonged into the postoperative period prevents stress response and platelet hyperaggregability after peripheral vascular surgery. *Eur J Vasc Surg*. 1994;8:395–400.
 54. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. *J Pain*. 2012;13:936–44.
 55. Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic postoperative pain: preoperative DNIC testing identifies patients at risk. *Pain*. 2008;138:22–8.
 56. Wilder-Smith OH, Schreyer T, Scheffer GJ, Arendt-Nielsen L. Patients with chronic pain after abdominal surgery show less preoperative endogenous pain inhibition and more postoperative hyperalgesia: a pilot study. *J Pain Palliat Care Pharmacother*. 2010;24:119–28.