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Treatment of Postmastectomy Pain With Ambulatory Continuous Paravertebral Nerve Blocks
A Randomized, Triple-Masked, Placebo-Controlled Study

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Background: We aimed to determine with this randomized, triple-masked, placebo-controlled study if benefits are afforded by adding a multiple-day, ambulatory, continuous ropivacaine paravertebral nerve block to a single-injection ropivacaine paravertebral block after mastectomy.

Methods: Preoperatively, 60 subjects undergoing unilateral (n = 24) or bilateral (n = 36) mastectomy received either unilateral or bilateral paravertebral perineural catheter(s), respectively, inserted between the third and fourth thoracic transverse process(es). All subjects received an initial bolus of ropivacaine 0.5% (15 mL) via the catheter(s). Subjects were randomized to receive either perineural ropivacaine 0.4% or normal saline using portable infusion pump(s) [5 mL/h basal; 300 mL reservoir(s)]. Subjects remained hospitalized for at least 1 night and were subsequently discharged home where the catheter(s) were removed on postoperative day (POD) 3. Subjects were contacted by telephone on PODs 1, 4, 8, and 28. The primary end point was average pain (scale, 0–10) queried on POD 1.

Results: Average pain queried on POD 1 for subjects receiving perineural ropivacaine (n = 30) was a median (interquartile) of 2 (0–3), compared with 4 (1–5) for subjects receiving saline (n = 30; 95% confidence interval difference in medians, −4.0 to −0.3; $P = 0.021$). During this same period, subjects receiving ropivacaine experienced a lower severity of breakthrough pain (5 [3–6] vs 7 [5–8]; $P = 0.046$) as well. As a result, subjects receiving perineural ropivacaine experienced less pain-induced physical

and emotional dysfunction, as measured with the Brief Pain Inventory (lower score = less dysfunction): 14 (4–37) versus 57 (8–67) for subjects receiving perineural saline ($P = 0.012$). For the subscale that measures the degree of interference of pain on 7 domains, such as general activity and relationships, subjects receiving perineural saline reported a median score 10 times higher (more dysfunction) than those receiving ropivacaine (3 [0–24] vs 33 [0–44]; $P = 0.035$). In contrast, after infusion discontinuation, there were no statistically significant differences detected between treatment groups.

Conclusions: After mastectomy, adding a multiple-day, ambulatory, continuous ropivacaine infusion to a single-injection ropivacaine paravertebral nerve block results in improved analgesia and less functional deficit during the infusion. However, no benefits were identified after infusion discontinuation.

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Within the United States alone, more than 3 million women are living with a history of breast cancer[1]; approximately 100,000 new cases are diagnosed annually[1,2]; and 30% to 40% of women with this diagnosis undergo mastectomy.[2] Pain after mastectomy is often severe, with breakthrough pain as measured with a Numeric Rating Scale (NRS; 0-10, 0, no pain; 10, worst imaginable)[3] a median (interquartile) of 7 (4–8); and 25% of women describing a "continuous aching pain" the day after surgery.[4] Analgesia may be provided with a single-injection paravertebral nerve block, which involves the placement of long-acting local anesthetic adjacent to the peripheral nerves that innervate the breast.[4] Unfortunately, the longest-acting local anesthetics clinically available usually have a duration of less than 24 hours.[5]

In contrast, local anesthetic delivery may be continued indefinitely via a percutaneously inserted perineural catheter—termed a *continuous peripheral nerve block*—which has been demonstrated to reduce appreciably postoperative pain and opioid use in multiple other anatomic locations.[6] Therefore, the primary aim of this randomized, triple-masked (subjects, investigators and all clinical staff, statisticians), placebo-controlled study was to determine if postoperative benefits are afforded after mastectomy by adding a multiple-day, ambulatory, continuous ropivacaine infusion to a single-injection ropivacaine paravertebral nerve block. The primary end point was average postoperative pain level queried the day after surgery.

METHODS

Enrollment

The local institutional review board (University California San Diego, San Diego, CA) approved all study procedures, and all study subjects provided written, informed consent. The trial was prospectively registered at clinicaltrials.gov (NCT01231204). Patients offered enrollment included women 18 years or older

undergoing unilateral or bilateral mastectomy with or without axillary lymph node dissection, and desiring a single-injection paravertebral nerve block(s) for postoperative analgesia. Exclusion criteria included morbid obesity (body mass index > 40 kg/m^2); renal insufficiency (creatinine > 1.5 mg/dL), current chronic analgesic therapy (daily use > 4 weeks), a history of opioid dependence, pregnancy, incarceration, an inability to communicate with the investigators or hospital staff, or comorbidity that resulted in moderate or severe functional limitation (American Society of Anesthesiologists physical status classification > 2).

Catheter Insertion

All subjects had a peripheral intravenous catheter inserted, standard noninvasive monitors applied, supplemental oxygen administered via a face mask; and were placed in a seated position with their forehead resting on the forearms which were crossed and resting on a pillow atop a medical table. Intravenous midazolam and fentanyl were titrated for patient comfort, while ensuring that patients remained responsive to verbal cues. The catheter insertion site(s) was cleansed with chlorhexidine gluconate and isopropyl alcohol, and a clear, sterile, fenestrated drape applied. For all subjects, each target paravertebral space was located using ultrasound guidance. With a low-frequency (5-2 MHz) curved array transducer (C60x MicroMaxx; SonoSite Inc, Bothell, Washington) in a sterile sleeve, the paravertebral space between the third and fourth thoracic vertebrae was identified in a parasagittal view approximately 3 cm lateral to midline on the side of surgery. A local anesthetic skin wheal was raised caudal to the ultrasound transducer. An 8.9-cm, 17-gauge, Tuohy-tip needle (FlexTip Plus; Arrow International, Reading, Pennsylvania) was inserted through the skin wheal in-plane beneath the ultrasound transducer and directed to the paravertebral space. Normal saline (5 mL) was injected via the needle to help open the paravertebral space and observe the pleura being displaced anteriorly. A perineural catheter was inserted 2 to 4 cm beyond the needle tip, the needle withdrawn over the catheter, the catheter affixed with an occlusive sterile dressing, (paper) taped directly caudal and then lateral above the iliac crest, and the injection port subsequently affixed with an anchoring device lateral to the navel on the ipsilateral side.

Fifteen milliliters of 0.5% ropivacaine with epinephrine, 5 μg/mL, was slowly injected via the catheter with gentle aspiration every 3 mL. Catheter placement was considered successful if, within 30 minutes, the patient experienced any decreased sensation to cold temperature with an alcohol pad over the approximate level of the ipsilateral third thoracic dermatome. Misplaced catheters were replaced successfully, or the patient excluded from further study participation. For subjects undergoing bilateral mastectomy, a catheter using the same protocol was subsequently inserted on the contralateral side.

Randomization

Treatment allocation occurred after confirmation of successful insertion of the perineural catheter(s). Subjects were randomized to 1 of 2 groups: Placebo (normal saline) or ropivacaine (0.4%). Randomization was carried out by investigational pharmacists using computer-generated lists. Pharmacists provided portable, elastomeric infusion pumps (LV5 Infusor; Baxter International Inc, Deerfield, Illinois) with a fixed rate of 5 mL/h and 300 mL reservoir, filled with study solution as determined by these lists. Subjects were assigned to a treatment in sequential order, and randomization was stratified both by procedure (unilateral or bilateral mastectomy) as well as lymph node dissection (with or without). Subjects having a bilateral mastectomy received 2 separate infusion pumps, each affixed to a separate catheter, and always containing the identical solution (all subjects received only 1 treatment: ropivacaine or normal saline). Subjects, investigators, observers, statisticians, and all clinical staff were masked to treatment-group assignment.

Perineural infusion was initiated within the operating room. Intraoperatively, all subjects received a general anesthetic using inhaled anesthetic and oxygen. Intravenous fentanyl was administered for cardiovascular responsiveness to noxious stimuli at the discretion of the anesthesia provider.

For postoperative analgesia, all subjects received the single-injection ropivacaine paravertebral block (initiated via the catheter), and oral acetaminophen (975 mg 4 times daily). Administration of rescue analgesics for breakthrough pain was determined by pain severity using the NRS: oxycodone 5 mg (NRS < 4) or 10 mg (NRS ≥ 4). While hospitalized, pain was reassessed 30 minutes later and intravenous morphine (2–4 mg) was repeated every 30 minutes until the NRS is less than 4.

Subjects remained hospitalized at least 1 night, and were subsequently discharged home with their perineural catheter(s) in situ. Subjects and their caretakers were provided with verbal and written catheter/pump instructions, the telephone and pager numbers of an investigator available at all times, and prescriptions for their outpatient oral medications that did not differ from the oral analgesics provided in the hospital. Subjects were telephoned in the afternoons of postoperative days (PODs) 1 and 2, and the morning of POD 3, at which time subjects' caretakers removed the perineural catheter(s) with physician instructions provided by telephone.

Outcome Measurements (End Points)

Data were collected in person preoperatively, extracted from computerized records during hospitalization (recovery room and from 00:00 to 12:00 on POD 1), and recorded by telephone on PODs 1, 4, 8, and 28. Staff masked to treatment group assignment performed all assessments. We selected outcome measures that have established reliability and validity, with minimal interrater discordance, and are recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement.[7] The primary instrument was the Brief Pain Inventory (short form) administered on PODs 1, 4, 8, and 28.[8,9] This instrument assesses pain and its interference with physical and emotional functioning within the previous 24 hours. There are 3 domains, namely, (1) pain, with 4 questions involving "worst," "average," "least," and "current" pain levels using the NRS; (2) percentage of relief provided by pain treatments with 1 question; and, (3) interference with physical and emotional functioning using a 0–10 Likert scale (0, no interference; 10, complete interference). The 7 interference questions involve general activity, mood, walking ability, normal work activities inside and outside of the home, relationships, sleep, and enjoyment of life.[10,11] The 4 pain scores were combined to produce a pain subscale (0–40), and the 7 functioning questions combined to produce an interference subscale (0–70). Values for the entire Brief Pain Inventory (0, optimal; 120, worst possible) consist of both of these subscales combined with the question involving relief provided by pain treatments (percentage relief divided by 10 and then subtracted from 10: 0, complete relief; 10, no relief). The use of both single items (eg, average pain) and the composite scores is supported by the IMMPACT recommendations for assessing pain in clinical trials.[12–14]

Additional information was gathered after the Brief Pain Inventory, including the incidence and intensity (measured on the NRS) of phantom breast pain, defined as painful sensations
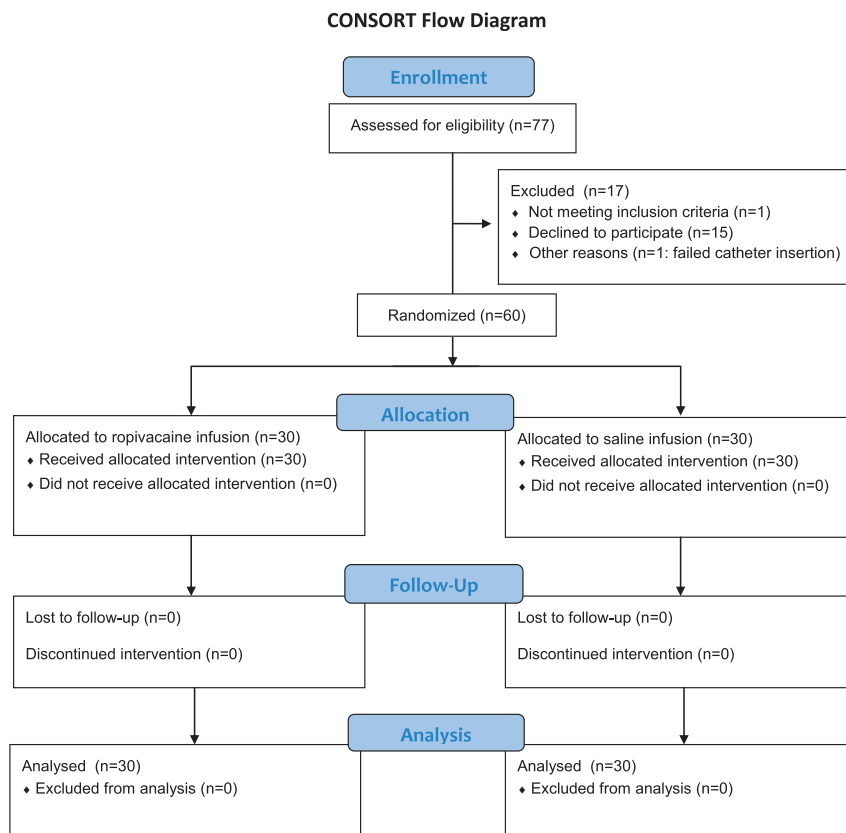
CONSORT Flow Diagram

FIGURE 1. CONSORT flowchart.

perceived within breast tissue after surgical resection.[15] Also assessed was any difficulty sleeping because of pain (binary variable: yes or no), the perceived number of awakenings due to pain, and nausea using a 0–10 Likert scale (0, no nausea; 10, vomiting).[16]

Statistical Analysis

Sample size calculations were centered around the hypothesis that a multiple-day, ambulatory, continuous paravertebral block decreases the incidence and severity of postmastectomy pain in the week after surgery. To this end, the primary end point was the difference between the 2 treatment groups in average NRS (as administered as part of the Brief Pain Inventory) queried on the day after surgery. Given an n = 60 with subjects equally distributed between the 2 treatment groups, assuming a standard deviation of 2 for the primary end point (based on unpublished data), and a 2-sided type I error protection of 5%, we had 80% power to detect a difference between means of 1.5 (StatMate; GraphPad Software, San Diego, California). No adjustments were made for multiple comparisons, and significant findings in secondary outcomes should be viewed as suggestive, requiring confirmation in a future trial before considering them as definitive.

Normality of distribution was determined using the Shapiro-Wilk test.[17] For normally distributed and nonparametric data, single comparisons were made using a 2-sample *t* test or Mann-Whitney *U* test, respectively. Categorical data were analyzed using the χ^2 test with Yates continuity correction, or Fisher exact test if expected cell counts were below 5. $P < 0.05$ was considered significant. Count data (eg, incidence of phantom pain, number

of awakenings due to surgical pain, incidence of wound pain, and opioid dose) were analyzed with a Negative Binomial generalized linear model, with group as a categorical covariate. Models were fit by the glm.nb () command from the R package MASS.[18] If the model is found to be inappropriate, then a zero-inflated Negative Binomial model is considered as an alternative, with a binomial generalized linear model with group as a covariate for the zero-inflation. Zero-inflated Negative Binomial models are fit by the zeroinfl () command from the R package pscl.[‖] The nonnested hypothesis test of Vuong[19] was used for selecting between Negative Binomial and Zero-inflated Negative Binomial models, with $\alpha = 0.05$ used as the decision criterion. These analyses were executed using R version 2.12 (2010),[#] and performed according to the intention-to-treat principle.[20]

RESULTS

During a 24-month period beginning in December 2010, 61 subjects enrolled, and all but 1 (98%) had unilateral (n = 24) or bilateral (n = 36) catheter(s) inserted successfully per protocol

TABLE 1. Population Data and Procedural Information

Perineural Infusion	Ropivacaine (n = 30)	Placebo (n = 30)
Age, y	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) or number of subjects, as indicated.

(Fig. 1; Table 1). Of the 60 remaining subjects, 24 received unilateral and 36 bilateral catheter(s).

Primary End Point

Average pain queried on POD 1 for subjects receiving ropivacaine (n = 30) was a median (interquartile) of 2 (0–3), versus 4 (1–5) for subjects receiving saline (n = 30; 95% confidence interval difference in medians, −4.0 to −0.3; $P = 0.021$).

Secondary End Points

Similarly, during the infusion period on POD 1 (Table 2), subjects receiving ropivacaine experienced a lower severity of breakthrough pain (5 [3–6] vs 7 [5–8]; $P = 0.046$); and, reported less pain-related interference with physical and emotional functioning (Table 3). For example, for the interference subscale that measures the degree of interference of pain on physical and emotional functioning, subjects receiving perineural saline reported a median score 10 times higher than those receiving ropivacaine (3 [0–24] vs 33 [0–44]; $P = 0.035$). In contrast, after infusion discontinuation, there were no statistically significant differences detected between treatment groups (Tables 4 and 5).

Protocol Deviations and Adverse Events

One subject receiving perineural ropivacaine via bilateral catheters requested removal of one of the catheters that "pinched" at the skin the evening of POD 0; and, subsequently requested removal of the contralateral catheter and study withdrawal the following afternoon for the same reason. The discomfort resolved immediately upon catheter withdrawal and did not recur. For purposes of analysis, this subject was retained within her treatment group until the time of study withdrawal, per both the intention-to-treat principle and United States ethical guidelines.[20,21] Of note,

there were no unintended catheter dislocations. Another subject had a catheter inserted on the incorrect side for a unilateral mastectomy before randomization, and this catheter was withdrawn and a new catheter inserted on the correct side.

One subject with bilateral catheters infusing normal saline experienced contact dermatitis in skin areas with adhesive exposure (occlusive dressing, paper tape, and anchoring device), which resolved after per-protocol catheter removal on POD 3. Another subject exhibited a bilateral block from the first through tenth thoracic dermatome after the initial unilateral ropivacaine injection, suggesting epidural spread. She did not exhibit hypotension and elected to remain in the study. All signs of the regional block had resolved within 12 hours, and after study group assignment unmasking, it was revealed that she had received perineural normal saline.

DISCUSSION

This randomized, triple-masked, placebo-controlled study provides evidence that, after unilateral or bilateral mastectomy, adding a multiple-day, ambulatory, continuous ropivacaine

TABLE 2. Secondary End Points

Perineural Infusion	Ropivacaine (n = 30)	Placebo (n = 30)	*P*
Pain (NRS POD 1 00:00–12:00)*	3.6 (2.0–4.0)	3.7 (2.5–4.6)	0.183
Morphine equivalents (mg)*			
Intraoperative*	3.0 (2.5–4.5)	2.5 (2.5–5.0)	0.752
Recovery room*	1.0 (0.0–2.8)	2.4 (1.0–5.5)	0.013
POD 1 (00:00–12:00)*	1.5 (0.0–8.5)	3.3 (1.4–10.3)	0.402
Oral opioid (oxycodone, mg)			
POD 4	10 (0–23)	10 (0–20)	0.376
POD 8	1 (0–14)	0 (0–8)	0.840
Nausea (0–10; 10, vomiting)			
POD 1*	0 (0–0)	0 (0–6)	0.053
POD 4	0 (0–0)	0 (0–0)	0.277
POD 8	0 (0–0)	0 (0–0)	0.294
Difficulty sleeping (no. subjects)			
POD 1*	9	16	0.116
POD 4	8	8	1.000
POD 8	10	8	0.848
POD 28	6	6	>0.999
Awakenings due to pain (no. subject)			
POD 1*	0 (0–1)	1 (0–3)	0.306
POD 4	0 (0–1)	0 (0–1)	0.828
POD 8	0 (0–2)	0 (0–0)	0.127
POD 28	0 (0–0)	0 (0–0)	0.445

Values represent the previous 24 h from time queried, unless otherwise indicated.

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

Oral opioid and nausea queried exclusively on POD 4/8 and 1/4/8, respectively.

*During perineural infusion.

TABLE 3. Brief Pain Inventory During the Perineural Infusion

POD	1		
	Ropivacaine	Placebo	*P*
Pain (0–10 NRS)			
Worst	5 (3–6)	7 (5–8)	0.046
Average	2 (0–3)	4 (1–5)	0.021
Least	0 (0–2)	2 (0–3)	0.053
Current	1 (0–4)	4 (0–5)	0.050
Pain subscale total (0–40)	9 (4–13)	16 (7–21)	0.021
Relief provided by analgesics (%)	90 (60–100)	50 (30–100)	0.060
Interference with (0–10; 0, none)			
General activity	1 (0–5)	6 (0–8)	0.052
Mood	0 (0–2)	3 (0–6)	0.038
Walking	0 (0–2)	3 (0–5)	0.046
Work (inside/outside of home)	0 (0-4)	5 (0–8)	0.017
Relationships	0 (0–1)	3 (0–6)	0.017
Sleep	0 (0–2)	3 (0–8)	0.034
Enjoyment of life	0 (0–5)	5 (0–8)	0.049
Interference subscale total (0–70)	3 (0–24)	33 (0–44)	0.035
Brief Pain Inventory total (0–120)	14 (4–37)	57 (8–67)	0.012

Values are reported as median (interquartile) and represent the time between the surgical procedure and the time queried.

Values for the Brief Pain Inventory total score (0, optimal; 120, worst possible) consist of the 2 subscales combined with the question involving relief provided by pain treatments (percentage relief divided by 10 and then subtracted from 10: 0, complete relief; 10, no relief).

infusion to a single-injection ropivacaine paravertebral nerve block results in improved analgesia and decreased functional deficit the day after surgery. In contrast, after the end of the infusion, there were no benefits detected from the additional continuous paravertebral block. Given the tens-of-thousands of patients undergoing mastectomy within the United States alone,[1,2] these results have broad clinical implications, not only for immediate postoperative analgesia, but potentially persistent postoperative pain as well.

Benefits of continuous peripheral nerve blocks have been documented for various anatomic catheter locations,[6] so while it might seem self-evident that paravertebral perineural infusions would provide similar benefits after mastectomy, there are good reasons to not infer this causal relationship from studies involving other anatomic sites. Importantly, mastectomy involves many thoracic levels, and the often-accompanying axillary dissection extends involvement to the lower cervical levels. There is robust, prospectively collected evidence that the vertical spread of local anesthetic resulting from a single injection is greatly limited: a mean (SD) of 3.0 (1.2) dermatomes with a single bolus injection (0.26 mL/kg of local anesthetic plus 0.1 mL/kg of radiopaque dye) compared with 6.5 (2.0) dermatomes with 4 individual bolus injections (each with 25% of the volume) at 4 consecutive thoracic levels.[22] Furthermore, with the relatively low volume (5–10 mL/h), dose (20–40 mg/h), and injection pressure of a perineural infusion compared with a single-injection bolus via a Tuohy needle, it is doubtful that a continuous paravertebral block affects more levels than a single-injection bolus.

Previously Published Literature

There is an abundance of published evidence that single-injection paravertebral blocks improve postmastectomy analgesia.[4,23–25] In addition, multiple studies have documented improved analgesia and/or decreased supplemental opioid requirements associated with a continuous paravertebral block.[23,26–30] However, all but 1 of these latter investigations included a long-acting single-injection paravertebral block in addition to the perineural infusion, whereas the control group received neither a single-injection nor perineural infusion.[23,26–29] Since the analgesic effects of a single-injection paravertebral block have been documented as long as 72 hours,[5] it remained unknown if the benefits cited in the perineural infusion studies were due exclusively to the single-injection block, or perineural infusion as well.[23,26–29] And, in fact, the only published study including a control group with an active single-injection block failed to detect any benefits from adding a 72-hour ropivacaine perineural infusion.[30] In this respect, the current study is the first randomized, controlled trial demonstrating that postmastectomy patients benefit from a paravertebral local anesthetic infusion.[6] There are multiple potential reasons why the current results differed from this previously published investigation,[30] including differences in technique of the initial paravertebral block and catheter-insertion, ropivacaine infusion concentration/rate, and inclusion of a non-steroidal anti-inflammatory drug (naproxen) beginning the day after surgery in the previous study.

As with all medical interventions, perineural local anesthetic infusion has intrinsic risks that must be balanced against the potential benefits. This study's results suggest there are benefits in providing a continuous paravertebral nerve block after mastectomy, but the infusion-related adverse events must not be overlooked or minimized. In our study, subjects experienced contact dermatitis from adhesive exposure, catheter "pinching" at the skin, bilateral block suggesting possible epidural spread, and catheter insertion on the incorrect side. In addition, both in-hospital and ambulatory perineural infusion require a system for management that may not be available at every practice.

Patient-Oriented Outcomes

Simple pain scores and recognition of the importance of patient-oriented outcomes (eg, health-related quality of life,[31] quality of recovery,[32] global outcome measures of function[33]) have greatly increased over the last decade, both to improve the quality of healthcare and to provide value data (eg, cost-benefit analysis) for external organizations such as government agencies and insurance companies that increasingly require evidence of performance.[34] For these reasons, we administered the Brief Pain Inventory—an instrument assessing pain and its interference on physical and emotional functioning—for the present study[8,9] and documented dramatically decreased pain-related physical and emotional functional interference during a perineural local anesthetic infusion. To date, few studies involving continuous peripheral nerve blocks have examined quality-of-life measures, and there is a conspicuous lack of evidence in documented improvements of global measures during perineural infusion.[6]

Persistent Postoperative Pain

Chronic postsurgical pain is a well-documented risk after mastectomy.[35] In 1 study, the addition of a single-injection paravertebral block decreased the intensity of motion-related pain 4 weeks after surgery ($P = 0.005$).[36] In a second investigation, a single-injection paravertebral block followed by 48 hours

TABLE 4. Brief Pain Inventory After the Perineural Infusion

	4		8		28	
POD	Ropivacaine	Placebo	Ropivacaine	Placebo	Ropivacaine	Placebo
Pain (0–10 NRS)						
Worst	4 (1–6)	5 (2–6)	3 (1–5)	3 (1–5)	1 (0–4)	2 (0–3)
Average	3 (0–3)	2 (0–4)	2 (0–3)	2 (0–3)	0 (0–2)	0 (0–1)
Least	0 (0–3)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–0)	0 (0–0)
Current	2 (0–3)	2 (0–4)	1 (0–3)	1 (0–3)	0 (0–1)	0 (0–0)
Pain subscale total (0–40)	10 (2–13)	8 (3–15)	6 (1–12)	7 (2–12)	1 (0–9)	3 (0–5)
Relief provided by analgesics (%)	80 (50–100)	70 (50–100)	90 (55–100)	85 (60–100)	100 (90–100)	100 (85–100)
Interference with (0–10)						
General activity	3 (0–6)	3 (0–7)	1 (0–4)	3 (0–6)	0 (0–2)	0 (0–3)
Mood	1 (0–3)	0 (0–4)	0 (0–3)	0 (0–4)	0 (0–1)	0 (0–1)
Walking	0 (0–2)	0 (0–3)	0 (0–1)	0 (0–2)	0 (0–0)	0 (0–0)
Work (inside/outside of home)	3 (0–7)	1 (0–6)	1 (0–4)	0 (0–4)	0 (0–2)	0 (0–3)
Relationships	0 (0–2)	0 (0–3)	0 (0–2)	0 (0–2)	0 (0–1)	0 (0–0)
Sleep	0 (0–4)	0 (0–5)	0 (0–5)	0 (0–4)	0 (0–2)	0 (0–1)
Enjoyment of life	3 (0–5)	0 (0–5)	0 (0–3)	0 (0–5)	0 (0–1)	0 (0–2)
Subscale total (0–70)	14 (0–26)	12 (0–32)	6 (0–22)	3 (0–22)	0 (0–12)	0 (0–11)
Brief Pain Inventory total (0–120)	31 (2–40)	24 (4–53)	15 (2–40)	20 (3–43)	0 (0–11)	3 (0–12)

There were no statistically significant differences between treatment groups.

Values are reported as median (interquartile) and represent the previous 24 h from time queried.

Values for the Brief Pain Inventory total score (0, optimal; 120, worst possible) consist of both subscales combined with the question relief provided by analgesics calculated as follows: percentage relief divided by 10 and then subtracted from 10 (0, complete relief; 10, no relief).

of infusion decreased the prevalence of pain 10 weeks postoperatively from 80% (control group) to 0% (*P* = 0.009).[26] Of note, the control groups for both of these studies received no regional anesthetic/analgesic, so it remains unknown if the benefits of the latter are related to the perineural infusion or exclusively the initial surgical block.[26] In the current study, subjects who received a ropivacaine perineural infusion in addition to a single-injection block reported a maximum ("worst") NRS at 4 weeks of a median (interquartile) of 0.5 (0.0–3.5) compared with 2.0 (0.0–3.0) for subjects with only a single-injection block (and little difference in opioid use after the infusion). This difference did not reach statistical significance (*P* = 0.305); and, the average and least pain scores at 4 weeks were exceptionally low for both groups (Table 4), suggesting that the single-injection surgical block is of primary importance in decreasing the risk of persistent postsurgical pain relative to the subsequent perineural infusion.

Reports of the prevalence of postmastectomy phantom breast pain—painful sensations perceived in the breast that is no longer present—range from 14% to 44% in patients provided traditional opioid postoperative analgesics.[35] To our knowledge, the association between paravertebral blocks/infusions and this pain phenomenon has not been previously investigated. However, data involving upper- and lower-extremity amputation suggest that continuous peripheral nerve blocks may decrease the incidence and/or severity of phantom limb pain.[6,37,38] When a nerve is severed, evidence indicates that the bombardment of the peripheral and central nervous system with nociceptive signals results in changes to the spinal cord, thalamus, and cerebral cortex.[39] In an uncontrolled series of 19 patients with phantom limb pain treated with continuous peripheral nerve blocks in the immediate postamputation period, pain intensity decreased by approximately 50% at 1 and 6 months.[40] Although our study failed to detect any trend of decreased phantom breast pain prevalence or severity in

TABLE 5. Phantom Breast Pain

Perineural Infusion	Ropivacaine (n = 30)	Placebo (n = 30)	*P*
Prevalence (no. subjects reporting pain)			
POD 1	0	1	>0.999
POD 4	1	2	>0.999
POD 8	3	3	>0.999
POD 28	5	5	>0.999
Incidence (times per day for each subject)			
POD 1	0 (0–0)	0 (0–0)	*
POD 4	0 (0–0)	0 (0–0)	0.560
POD 8	0 (0–2)	0 (0–0)	0.632
POD 28	0 (0–2)	0 (0–2)	0.875
Severity (*Worst* NRS previous 24 h)			
POD 1	0 (0–0)	0 (0–0)	*
POD 4	0 (0–0)	0 (0–0)	0.543
POD 8	0 (0–1)	0 (0–0)	0.674
POD 28	0 (0–4)	0 (0–0)	0.855
Severity (*Average* NRS previous 24 h)			
POD 1	0 (0–0)	0 (0–0)	*
POD 4	0 (0–0)	0 (0–0)	0.543
POD 8	0 (0–1)	0 (0–0)	0.611
POD 28	0 (0–1)	0 (0–1)	0.650

Values for pain severity are reported as median (10th–90th percentiles).

*A *P* value could not be calculated due to only one nonzero datum.

the active treatment group (Table 5), it was also not powered for these secondary end points.

Study Limitations

This investigation has several limitations. First, we provided exclusively a basal infusion of 5 mL/h (ropivacaine 0.4%, or 20 mg/h), without patient-controlled bolus doses. The optimal delivery regimen for paravertebral infusions remains unknown; and, therefore, a higher basal infusion rate (>5 mL/h) and/or local anesthetic concentration (>0.4%) than used in this study may yield superior results. In a previous study involving continuous paravertebral blocks providing a basal dose similar to the present investigation (levobupivacaine 0.2% at 8 mL/h, or 16 mg/h) combined with patient-controlled bolus doses (3 mL with 15-minute lockout), subjects triggered their bolus a mean (SD) of 72 (16) times in the 36 hours after mastectomy.[41] These results suggest that providing patient-controlled bolus doses in the present study may have improved analgesia and produced even greater differences between the 2 treatment groups.[42] Since the current study evaluated 1 perineural delivery regimen on various postmastectomy end points, it does not provide data to support any specific recommendations on the optimal basal rate, local anesthetic concentration, inclusion of a bolus dose, bolus dose volume, or optimal lockout duration. Relatedly, nonsteroidal anti-inflammatory 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 within the 2 treatment groups.[43,44]

In addition, although the overwhelming number of investigations—including the present study—involving breast surgery and paravertebral infusion included the third thoracic level for catheter insertion,[23,26–30,41,45] the optimal level for mastectomy remains unknown. Furthermore, although the current study provides evidence that a continuous paravertebral block provides benefits through the day after surgery, we did not collect data on pain on POD 2 or 3. Therefore, it remains unknown what the optimal duration of infusion is after mastectomy. However, we suspect that this case is much like catheters in most other anatomic locations: the intensity and duration of pain are highly variable, and a subset of patients benefits from a more prolonged infusion whereas others require no infusion at all.[6] Lastly, we did not measure blood levels of nociceptive processing or stress response markers that could have helped elucidate any association between perioperative analgesia, and persistent postoperative pain and cancer recurrence.[26,46]

In summary, this investigation provides evidence that after mastectomy, adding a multiple-day, ambulatory, continuous ropivacaine infusion to a single-injection ropivacaine paravertebral nerve block results in improved analgesia with less functional deficit during the infusion.

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