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Ambulatory continuous peripheral nerve blocks to treat postamputation phantom limb pain: a multicenter, randomized, quadruple-masked, placebo-controlled clinical trial

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Abstract

Phantom limb pain is thought to be sustained by reentrant neural pathways, which provoke dysfunctional reorganization in the somatosensory cortex. We hypothesized that disrupting reentrant pathways with a 6-day-long continuous peripheral nerve block reduces phantom pain 4 weeks after treatment. We enrolled patients who had an upper- or lower-limb amputation and established phantom pain. Each was randomized to receive a 6-day perineural infusion of either ropivacaine or normal saline. The primary outcome was the average phantom pain severity as measured with a Numeric Rating Scale (0-10) at 4 weeks, after which an optional crossover treatment was offered within the following 0 to 12 weeks. Pretreatment pain scores were similar in both groups, with a median (interquartile range) of 5.0 (4.0, 7.0) for each. After 4 weeks, average phantom limb pain intensity was a mean (SD) of 3.0 (2.9) in patients given local anesthetic vs 4.5 (2.6) in those given placebo (difference [95% confidence interval] 1.3 [0.4, 2.2], $P = 0.003$). Patients given local anesthetic had improved global impression of change and less pain-induced physical and emotional dysfunction, but did not differ on depression scores. For subjects who received only the first infusion (no self-selected crossover), the median decrease in phantom limb pain at 6 months for treated subjects was 3.0 (0, 5.0) vs 1.5 (0, 5.0) for the placebo group; there seemed to be little residual benefit at 12 months. We conclude that a 6-day continuous peripheral nerve block reduces phantom limb pain as well as physical and emotional dysfunction for at least 1 month.

Keywords: Continuous peripheral nerve blocks, Perineural local anesthetic infusion, Ambulatory analgesia, Chronic pain

1. Introduction

Tens-of-millions of people are living with a major limb amputation, and the prevalence is expected to double by 2050.[50] Although estimates vary greatly, 50% to 85% develop chronic, intractable pain perceived as being from the missing limb, a phenomenon termed "phantom limb pain."[24,44] This pain is frequently persistent[49] with chronic pain greatly increasing the risk of depression and decreasing quality of life and the chance of returning to work.[4] There are few adequately powered randomized clinical trials to guide treatment.[24,44]

The precise etiology of phantom pain remains unclear. Evidence suggests that severing a peripheral nerve induces changes in the spinal cord, thalamus, and somatosensory cortex, and this neural reorganization is positively correlated with the degree of phantom pain.[19] A single-injection peripheral nerve block in the amputated limb can result in short-term resolution of

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both the cortical abnormalities and phantom pain.[5] Unfortunately, when the single-injection nerve block resolves after a few hours, the phantom pain returns. But this intriguing result demonstrates that the abnormal mapping—and phantom pain—that occurs with amputation may not be permanent and may depend on continuous signaling from the peripheral nervous system.

Importantly, studies of chronic low back pain demonstrate that cortical thickness and cognitive abilities increased simultaneously 6 months after effective pain treatment.[45] These results establish that chronic pain-induced functional and structural brain abnormalities are not only reversible, but that treating chronic pain can restore normal brain function temporally remote from the intervention.[45] In other words, chronic phantom pain and cortical abnormalities may be maintained from abnormal peripheral input,[46] suggesting that a peripheral nerve block of extended duration—lasting days rather than hours—may allow prolonged cortical reorganization, thus providing lasting relief from phantom pain.

A week-long continuous peripheral nerve block may be reliably provided using a perineural local anesthetic infusion.[26] This technique involves the percutaneous insertion of a catheter adjacent to the peripheral nerve(s) supplying the affected limb. Local anesthetic is then infused through the catheter(s) without systemic side effects, permitting ambulatory administration using small, portable infusion pumps.[26] Numerous case reports of continuous blocks successfully treating established phantom pain have been published,[8,32,34,43,47] and results of a 3-patient randomized crossover pilot study were encouraging.[27]

We therefore designed this multicenter, randomized, quadruple-masked, placebo-controlled, parallel-arm clinical trial to determine if an ambulatory continuous peripheral nerve block of 6 days would provide effective and lasting analgesia for established upper- and lower-extremity postamputation phantom limb pain. Specifically, we tested the primary hypothesis that average phantom limb pain intensity is reduced 4 weeks after a 6-day perineural local anesthetic infusion.

2. Methods

This study followed Good Clinical Practice and was conducted within the ethical guidelines outlined in the Declaration of Helsinki. The trial was prospectively registered at clinicaltrials.gov (NCT01824082). The protocol was approved by the Institutional Review Board at each of the 4 enrolling centers as well as the United States Army Medical Research and Development Command Human Research Protection Office. An independent Data Safety Monitoring Board was responsible for the conduct and oversight of all aspects of the investigation from the planning phase through data analysis. Written, informed consent was obtained from all participants. Patients and the public were not directly involved in the development of this clinical trial.

2.1. Participants

Four medical centers enrolled patients, including public and private civilian, Veterans Affairs, and military treatment facilities. Enrollment was initially offered to adult patients of at least 18 years of age, with an upper- or lower-limb traumatic amputation occurring at least 12 weeks before presentation distal to the midhumerus or knee, respectively, and including at least one metacarpal or metatarsal bone, respectively. Due to low enrollment during the first year, inclusion criteria were revised to include surgical amputations and lower-extremity amputations distal to the hip (femoral head remaining). Participants had to experience phantom limb pain of at least a 2 or higher on the Numeric Rating Scale (NRS; 0-10, 0 = no pain; 10 = worst imaginable pain) at least 3 times each week for the previous 8 weeks; accept an ambulatory continuous peripheral nerve block for 6 days; avoid changes to their analgesic regimen from 4 weeks before and at least 4 weeks after the initial catheter placement; and have a "caretaker" who would transport the patient home after the catheter insertion(s), and remain with the patient for at least the first night of the infusion.

Patients were excluded if they had known renal insufficiency (elevated creatinine); allergy to study medications; pregnancy; incarceration; inability to communicate with the investigators; morbid obesity (body mass index greater than 40 kg/m^2); comorbidity that resulted in moderate-to-severe functional limitations; and contraindication to a continuous peripheral nerve block.

2.2. Catheter insertion

Patients fasted beginning midnight before catheter insertion. For women of childbearing age with the possibility of pregnancy, a sample of urine was collected before any study interventions to confirm a nonpregnant state. Study participation required that women of childbearing age with the possibility of pregnancy use a birth control method to prevent pregnancy during the study fluid administration. A peripheral intravenous catheter was inserted, standard noninvasive monitors applied (blood pressure cuff, pulse oximeter, 5-lead electrocardiogram), oxygen administered through a facemask, and midazolam and fentanyl (intravenous) titrated for patient comfort while ensuring responsiveness to verbal cues. Hair within the area(s) that would be subsequently covered by the catheter dressing(s) was removed with a surgical clipper, if necessary. The catheter insertion site(s) were cleansed with chlorhexidine gluconate and isopropyl alcohol, and a sterile, fenestrated drape applied. The amputation site dictated the anatomical location(s) and number of catheters: one infraclavicular catheter targeting the brachial plexus cords for upper-extremity amputations,[38] and a sciatic and femoral catheter for lower-extremity amputations.[37]

2.3. Upper-extremity amputation

Patients in a supine position had an infraclavicular perineural catheter inserted adjacent to the cords of the brachial plexus. With a low-frequency curvilinear array ultrasound transducer in a sterile sleeve, the brachial plexus and axillary artery were identified in a transverse cross-sectional (short axis) view. Once the optimal image of the brachial plexus cords was obtained, a local anesthetic skin wheal was raised cephalad to the ultrasound transducer. A 17 gauge, Tuohy-tip needle (FlexBlock; Teleflex Medical, Research Triangle Park, NC) was inserted through the skin wheal in-plane beneath the ultrasound transducer and directed caudad until the needle tip was between the axillary artery and the posterior brachial plexus cord. Normal saline was injected through the needle to open the perineural space and allow subsequent insertion of a flexible 19-gauge perineural catheter 5 cm beyond the needle tip. The needle was removed over the catheter, the catheter tunneled subcutaneously, and the catheter affixed using a liquid adhesive, occlusive dressings, and an anchoring device. Local anesthetic (30 mL, lidocaine 2% with epinephrine 2.5 μg/mL) was injected through the catheter in divided doses with frequent aspiration. Participants were allocated to treatment only after confirmation of a successfully inserted perineural catheter.

2.4. Lower-extremity amputation

Patients had 2 perineural catheters inserted: a femoral and sciatic. Catheters were inserted using a high-frequency linear or low-frequency curvilinear array ultrasound transducer in a sterile sleeve and the target nerves identified in a transverse cross-sectional (short axis) view: the sciatic nerve within the proximal popliteal fossa cephalad to the sciatic bifurcation (below knee amputations) or in the subgluteal position (for above knee amputations); and the femoral nerve at the inguinal crease. For each insertion, a local anesthetic skin wheal was raised lateral to the transducer, and a 17 gauge, Tuohy-tip needle (FlexBlock; Teleflex Medical) inserted through the skin wheal in-plane beneath the ultrasound transducer and directed medially until the needle tip was posterior to each target nerve. Normal saline was injected through the needle to open the perineural space allowing subsequent insertion of a flexible 19-gauge perineural catheter 5 cm beyond the needle tip for each nerve. The needle was removed over the catheter, the catheter tunneled subcutaneously, and the catheter affixed using a liquid adhesive, occlusive dressings, and an anchoring device. Local anesthetic (20 mL, lidocaine 2% with epinephrine 2.5 μg/mL) was injected through each catheter in divided doses with frequent aspiration. Participants were allocated to treatment only after confirmation of a successfully inserted perineural catheter.

2.5. Randomization and masking

Participants were randomized to either *ropivacaine 0.5%* or *saline* (placebo). Randomization was stratified by institution and amputation location (upper vs lower extremity) in a 1:1 ratio, and in randomly chosen block sizes of 2 to 6 for upper and 2 to 10 for lower extremities. Randomization lists were created using SAS by the University of California San Diego Investigational Drug Service and provided to the Investigational Drug Service at each of the enrolling centers which prepared all study solutions. Treatment group assignments were not released by the Investigational Drug Service until the conclusion of the trial (further details in the statistical section). Ropivacaine and normal saline are indistinguishable in appearance, and therefore all investigators, participants, and clinical staff were masked to treatment group assignment.

2.6. Study intervention

Portable, programmable, electronic infusion pumps (ambIT Preset Pump; Summit Medical, Salt Lake City, UT) were used to administer perineural study solution (1100 mL) at fixed rates for over 6 days: femoral 2.5 mL/h; sciatic 5 mL/h; and infraclavicular 7.5 mL/h.

Before discharge, participants and their caretakers were provided with verbal and written instructions as well as the contact information for an investigator available at all times. Patients were informed that the dense nerve block from the short-acting lidocaine bolus that they may be experiencing would regress, and that they should not be alarmed by any subsequent increase in pain. Patients with a lower-extremity amputation were provided with crutches and instructed to not weightbear using a prosthetic until the day after catheter removal due to a possible increased risk of falling. Patients were discharged home with their portable infusion pump(s) and perineural catheter(s) in situ.

If accidental premature dislodgement occurred, the patient could have the catheter replaced, if desired. All participants were retained in their respective treatment groups for analysis per the intent to treat principle. After fluid reservoir exhaustion, subjects or their caretakers removed catheters at home with instructions given by telephone then provided verbal confirmation that the demarcated catheter tip was intact; but, if a patient desired, they could opt to return to the enrolling center for catheter removal by an investigator. This procedure encompassed simply removing the occlusive dressing and gently pulling on the exposed perineural catheter.

2.7. Optional crossover treatment

Four to 16 weeks after randomization, patients could return for an optional perineural catheter insertion ("crossover"), and receive 6 days of ambulatory infusion with the alternate study solution (either ropivacaine 0.5% or normal saline), again in a double-masked fashion using the same protocol as described for the initial infusion. The funding agency required the primary outcome and optional crossover treatment to be moved from the original 12 weeks to 4 weeks after treatment so that participants would not have to wait 3 months to receive the crossover.

The main results of the study were provided to all participants after analysis.

2.8. Outcome measurements

We selected outcome measures that have established reliability and validity, with minimal interrater discordance, and are recommended for chronic pain clinical trials by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement.[15] Outcomes were evaluated at baseline (before infusion); on day 1 (during infusion); and on days 7, 14, 21, and 28 after the initial catheter insertion as well as any crossover insertions. Outcome measures were collected in person for the baseline measurements immediately before the initial catheter insertion as well as the crossover treatments. All other outcomes were collected by investigators at the University of California, San Diego by telephone regardless of enrolling center. Finally, patients were evaluated 6 and 12 months after the initial infusion to evaluate longer-term treatment effects.

The questionnaires differentiated multiple dimensions of limb sensations/pain:

(1) *Residual limb ("stump") pain:* Painful sensations localized to the portion of limb still physically present[35]
(2) *Phantom limb pain:* Painful sensations referred to the lost body part[35]
(3) *Phantom limb sensations:* Nonpainful sensations referred to the lost body part[35]

Each type of pain/sensation was defined for patients immediately before questionnaire application at each time point, and patients were instructed to address phantom limb pain when responding to questions unless otherwise specified. Each time the questionnaire was applied, participants were instructed to respond for the previous 3 days.[10] Exceptions included day 1 for both the initial and crossover treatments that occurred during the perineural infusions themselves because at these time points, the interest was in patients' experiences during the infusion, and not before catheter insertion. At these time points, participants were instructed to respond for the period since catheter insertion the previous day.

The primary instrument was the Brief Pain Inventory (short form), which assesses pain and its interference with physical and emotional functioning.[11] The form includes 3 domains: (1) *pain,* with 4 questions using an NRS to evaluate 4 pain levels: "current," "least," "worst," and "average" (primary outcome 4 weeks after the initial catheter insertion); (2) percentage of *relief* provided by

pain treatments with one question; and (3) *interference* with physical and emotional functioning using a 0 to 10 scale (0 = no interference; 10 = complete interference). The 7 interference questions involve general activity, mood, walking ability, normal work activities (both inside and outside of the home), relationships, sleep, and enjoyment of life.[11] The 7 functioning questions can be combined to produce an interference subscale (0-70). The use of both single items (eg, mood) and the composite scores is supported by the IMMPACT recommendations for assessing pain in clinical trials.[15,48] Because phantom limb and residual limb ("stump") pain have been correlated, the latter was assessed with the same 4 pain intensity questions.

To provide a global measure of worsening or improvement, the Patient Global Impression of Change (PGIC) was administered allowing patient evaluation of integrated treatment effects.[15] This measure is a 7-point ordinal scale requiring the patient to rate the current severity of phantom limb pain compared to their pretreatment baseline: 1 for "very much worse" to 7 for "very much improved" (4 is "no change"). Additional psychosocial factors were evaluated using the Beck Depression Inventory (BDI), a 21-item instrument measuring characteristic symptoms and signs of depression.[3] Each of the 21 factors is rated on a 0 to 3 scale, and then summed to produce the total score of 0 to 63. Mild, moderate, and severe depression are defined with scores of 10 to 18, 19 to 29, and 30 to 63, respectively.[16] Finally, the frequency and average duration of nonpainful phantom sensations as well as phantom and residual limb pain were assessed.

2.9. Statistical analysis

The investigators originally planned to unmask the treatment groups after the completion of the statistical analysis ("triple masked"); but after the analysis using "treatment A" and "treatment B" labels, opted to wait to unmask the groups until the manuscript was drafted ("quadruple masking"). After unmasking, the manuscript was not substantively changed. Randomized groups were compared on demographic and pain variables at baseline using descriptive statistics. Groups were considered well balanced on a particular baseline variable if the absolute standardized difference (difference in means, mean ranks, or proportions divided by the pooled SD) was less than $1.96\sqrt{(n_1+n_2)/(n_1n_2)} = 0.33$, where n_1 and n_2 are the per-group sample sizes.[1] All analyses were modified intention-to-treat, in which all randomized subjects who received any of the study treatment were included and retained in their respective treatment groups.[40] Confidence intervals (CIs) were adjusted for the group sequential design with overall alpha of 0.05, such that 95.6% CIs are reported throughout. We refer to them as "95% confidence intervals."

2.9.1. Aim 1: primary outcome

We assessed the average causal effect of a 6-day ambulatory continuous peripheral nerve block vs placebo on phantom limb pain intensity (average pain over the past 72 hours) at 4 weeks after the initial perineural catheter insertion and subsequent infusion using a multivariable linear regression model adjusting for clinical site, baseline average pain intensity, and any imbalanced baseline variables (baseline sleep score was the only imbalanced variable). Analogous linear regression models were conducted to assess the treatment effect on the change from baseline average pain intensity. We also assessed the treatment-by-clinical site interaction. The treatment effect was summarized as the least squares difference in means with interim-adjusted 95% CI, accounting for the group sequential design. Analogous linear regression models were conducted to assess the treatment effect on the change from baseline average pain intensity and for the tertiary outcomes of total pain score (patient sum of average, worst, least, and current pain), current pain, worst pain, and least pain for both phantom and residual limb pain.

2.9.2. Secondary outcomes

Regarding the secondary outcomes, the randomized groups were compared at 4 weeks on the global measure of improvement (PGIC scale; aim 2a) and BDI (aim 2c) using the Wilcoxon rank sum test and Hodges–Lehmann estimation of location shift between groups, stratified by study site. We assessed the treatment effect across the 7 components of the Brief Pain Inventory's pain interference using a mixed-effects regression model with a fixed effect for treatment and an unstructured correlation matrix adjusted for study site and baseline pain interference components (aim 2b).

2.9.2.1. Aim 2a

The randomized groups were compared on the global measure of improvement (PGIC scale) at 4 weeks using the Wilcoxon rank sum test and Hodges–Lehmann estimation of location shift between groups.

2.9.2.2. Aim 2b

We also assessed the treatment effect across the 7 components of the Brief Pain Inventory's pain interference using a mixed-effects regression model with a fixed effect for treatment and an unstructured correlation matrix. This model adjusted for study site, baseline pain interference components. The treatment-by-interference measure interaction was also tested. We also compared groups in the total interference score and the components using the Wilcoxon rank sum test and Hodges–Lehmann estimator of location shift and stratified by study site.

2.9.2.3. Aim 2c

Randomized groups were compared on BDI with the Wilcoxon rank sum test and estimated the treatment effect using the Hodges–Lehmann estimator of location shift, stratified by study site.

2.9.3. Tertiary outcomes

Randomized groups were compared on other 28-day phantom and residual limb pain outcomes (total score, worst pain, least pain, and current pain) using the Wilcoxon rank sum test and estimated the treatment effect using the Hodges–Lehmann estimator of location shift, stratified by study site.

2.9.4. Subgroup analysis

We assessed potential heterogeneity of the treatment effect within levels of 15 different baseline variables (ie, treatment-by-covariate interaction) using multivariable linear regression models adjusted for clinical site, baseline average pain intensity, and baseline sleep.

2.9.5. Missing data

For the primary outcome, we imputed missing values using the last-observation-carried-forward method as specified in our

protocol, assigning the most recent of available 14- or 21-day pain assessments. For those missing 14- and 21-day pain scores and other 28-day outcomes, we assigned the worst possible outcome to the treatment group and best possible outcome to the control group.

For other outcomes with missing 28-day values (and for the primary outcome as a sensitivity analysis), missing data were imputed by multivariable imputation with 5 imputation data sets. The imputation model included all the baseline variables listed in **Table 1** (except etiology and blinding assessment) together with all primary, secondary, and tertiary outcomes. All analyses were conducted with 5 imputed data sets; the parameter estimates (eg, coefficients and standard errors) obtained from each analyzed data set were combined to derive an overall effect estimate (CI) and *P*-value.

2.9.6. Assumptions

For all analyses, alternative statistical methods were used if the assumptions of the planned analyses were not met. For example, Mann–Whitney test or other nonparametric procedures were used instead of *t* test or linear regression if the assumptions of normality and/or equal variances were not met.

2.9.7. Blinding assessment

We assessed the quality of the blinding of subjects to initial treatment assignment by comparing the randomized groups on the proportion guessing correctly at 4 weeks (after measuring primary outcome pain scores) as to which group they were originally assigned. One of 5 choices was recorded, and included "definitely active," "probably active," "do not know," "probably placebo," and "definitely placebo." We used 2 common indices, the James Blinding Index (James BI)[28] and the Bang Blinding Index (Bang BI).[2] The older James BI gives a number between 0 and 1, in which higher values denote increasing levels of blindedness. It gives considerable weight to "don't know" responses, and only gives a single metric across both treatment and control groups. The more preferred Bang BI gives a single number between −1 and 1 for each treatment group, where 1 means completely unblinded, 0 means blinded, and −1 means the wrong treatment was consistently guessed. More weight is given to the more decisive responses.

2.9.8. Crossover phase

Beginning 4 to 16 weeks after the original randomization, requesting participants received the opposite treatment from that received in their original randomization, and the same measurements were collected for the following 4 weeks. This option allowed all subjects the opportunity to receive the study treatment. Because the crossover treatment was optional, it introduced selection bias from this time point forward. Because the crossover (second treatment) was voluntary, crossover was likely requested more often from those receiving placebo in the first phase. This does not preclude an estimate of the causal effect of treatment within these patients, but it does introduce selection bias and makes it difficult to interpret the results, although the comparisons are made within patient.

We assessed the treatment effect within the crossover patients using a linear mixed-effects regression model with a fixed effect for treatment and random effect for patient, adjusted for treatment sequence and period. We tested for evidence of differential carryover effect with the treatment-by-period interaction.

Importantly, we were able to estimate the variability of the individual causal effects of active treatment vs placebo using this crossover design. Variability of the individual causal effects cannot be directly estimated in a parallel group study (eg, from the main portion [aim 1] of this study we can only directly estimate the average causal effect) because only the outcome for the single treatment received is measurable for each subject. Therefore, estimation of the variability of the individual causal effects from the crossover portion of this trial, quantified as the SD of within-subject differences on treatment vs placebo, provides valuable information about the heterogeneity of the treatment effect across subjects associated with CPNB treatment of phantom limb pain. This is in addition to assessing treatment effect heterogeneity for the parallel group (main) part of this trial.

2.9.9. Long-term follow-up

Data for all outcomes were collected 6 and 12 months after randomization. Due to the crossover design, we were not able to directly assess the treatment effect of the active treatment vs placebo on these outcomes. Rather, we descriptively assessed the change from the initial baseline to both 6 and 12 months for those who were not crossed over—active and placebo, and those who were crossed over—initial active and placebo. No treatment effects were estimated.

2.9.10. Missing data

For participants missing 28-day data, we used the last-observation-carried-forward method if the brief pain inventory was measured at either 14 or 21 days. Otherwise, we used intent-to-treat and conservatively assigned the best observed score to the placebo group and the worst score for the treated group participants.

2.9.11. Interim analyses

We conducted interim analyses to assess efficacy (rejecting null) and futility (rejecting alternative) at each 25% of the maximum enrollment using a group sequential procedure. Specifically, a gamma spending function was used with parameters −4 and −2 for efficacy and futility, respectively.[25] Thus, boundaries at the first through fourth analyses for efficacy (futility in parentheses) were $P \leq 0.0016$ ($P > 0.9572$), $P \leq 0.0048$ ($P > 0.7186$), $P \leq 0.0147$ ($P > 0.2389$), and $P \leq 0.0440$ ($P > 0.0440$), respectively (Supplemental Figure A, available at http://links.lww.com/PAIN/B196).

2.9.12. Type I error

We used a parallel gatekeeping procedure to control the study-wide type I error at 0.05.[12] In the design phase, we prioritized the study outcomes into ordered sets, as aim 1, aim 2a, aim 2b, and then aim 2c. Analysis proceeded in that order, and testing proceeded through each "gate" to the next set if and only if at least one outcome in the current set reached significance. The significance level for each set was 0.044 times a cumulative penalty for nonsignificant results in the previous sets (ie, a "rejection gain factor" equal to the cumulative product of the proportion of significant tests across the preceding sets). Within a set, a multiple comparison procedure (Bonferroni correction) was used as appropriate to control the type I error at the appropriate level, if needed. SAS statistical software (Carey, North Carolina), R programming language (The R Project for Statistical Computing), and East 5.3 software (Cytel Inc) were used for all analyses.

Table 1

Initial treatment (n = 144).

	Active (n = 71)	Placebo (n = 73)	ASD
Demographics			
Age (y)	49 ± 14	50 ± 14	0.076
Female (%)	21 (30)	30 (41)	0.243
Body mass index (kg/m^2)	27 [25, 31]	27 [24, 33]	0.025
Marital status (%)*			0.151
Single (or divorced)	31 (44)	37 (51)	
Currently married	37 (52)	26 (36)	
Others (separated and widowed)	3 (4)	10 (14)	
Military status (%)			0.125
Civilian (never in military)	56 (79)	61 (84)	
Veteran	14 (20)	12 (16)	
Active duty	1 (1)	0 (0)	
Years of education	14 [12, 16]	13 [12, 16]	0.171
Amputation information			
Lower extremity (%)*	58 (82)	63 (86)	0.126
Above knee	28 (48)	24 (38)	
Below knee	30 (51)	39 (61)	
Upper extremity (%)	13 (18)	10 (14)	
Above elbow	11 (85)	8 (80)	
Below elbow	2 (15)	2 (20)	
Right (v. left) side (%)	32 (45)	37 (51)	0.113
Etiology			0.144
Traumatic amputation	20 (28)	16 (22)	
Surgical amputation due to:			
Cancer	5 (7)	5 (7)	
Infection	27 (38)	32 (44)	
Trauma	7 (10)	6 (8)	
Vascular deficiency	8 (11)	8 (11)	
Other	4 (6)	6 (8)	
Duration from amputation until randomization (mo)	52 [19, 104]	41 [16, 89]	0.145
History of residual limb pain (%)	50 (70)	57 (78)	0.176
Current residual limb pain (%)	40 (56)	48 (66)	0.194
Current prosthesis use (%)	50 (70)	60 (82)	0.279
Additional limb amputation(s) (%)	12 (17)	11 (15)	0.050
Brief pain inventory			
Phantom pain previous 3 d (numeric rating scale)			
Current	5.0 [2.0, 7.0]	5.0 [3.0, 7.0]	0.003
Least	2.0 [1.0, 4.0]	3.0 [2.0, 5.0]	0.144
Average	5.0 [4.0, 7.0]	5.0 [4.0, 7.0]	0.032
Worst	8.0 [8.0, 10]	8.0 [7.0, 10]	0.099
Residual limb pain previous 3 d (numeric rating scale)			
Current	1.0 [0, 4.0]	3.0 [0, 6.0]	0.173
Least	0 [0, 3.0]	2.0 [0, 4.0]	0.143
Average	3.0 [0, 5.0]	4.0 [1.0, 6.0]	0.209
Worst	5.0 [0, 8.0]	6.0 [2.0, 8.0]	0.104
Phantom pain relief from medication (%)*†		0.107	
0%-25%	26 (43)	22 (39)	
26%-50%	21 (35)	18 (32)	
51%-75%	5 (8)	13 (23)	
76%-100%	8 (13)	4 (7)	
Residual limb pain relief from medication (%)†		0.052	
0%-25%	23 (50)	19 (40)	
26%-50%	10 (22)	16 (34)	
51%-75%	5 (11)	9 (19)	
76%-100%	8 (17)	3 (7)	
Pain interference components			
General activity	6.0 [3.0, 8.0]	5.0 [3.0, 8.0]	0.028
Mood	6.0 [2.0, 9.0]	6.0 [4.0, 8.0]	0.025
Walking ability	5.0 [0, 9.0]	5.0 [2.0, 9.0]	0.097
Normal work	6.0 [3.0, 8.0]	5.0 [2.0, 8.0]	0.048

(*continued on next page*)

Table 1 (*continued*)

	Active (n = 71)	Placebo (n = 73)	ASD
Relations with other people	4.0 [0, 7.0]	4.0 [0, 7.0]	0.081
Sleep	8.0 [5.0, 9.0]	7.0 [4.0, 8.0]	0.355
Enjoyment of life	6.0 [2.0, 9.0]	6.0 [3.0, 8.0]	0.117
Depression			
Beck depression inventory	15 [4, 24]	14 [7, 24]	0.023
Beck depression category (%)			0.058
Minimal	25 (35)	30 (41)	
Mild	16 (23)	14 (19)	
Moderate	24 (34)	20 (27)	
Severe	6 (8.5)	9 (12)	
Pain immediately before and after initial local anesthetic bolus			
Phantom pain			
Immediately before	5.0 [3.0, 7.0]	5.0 [3.0, 7.0]	0.028
20 minutes after	0 [0, 2.0]	0 [0, 2.0]	0.015
Residual limb pain			
Immediately before	1.0 [0, 4.0]	3.0 [0, 5.0]	0.163
20 minutes after	0 [0, 0]	0 [0, 0]	0.016

Any variable with an absolute standardized difference (ASD) > 0.327 was considered unbalanced.
* Totals not equal to 100% due to rounding error.
† Number of missing values for active and control groups are 11, 16 (phantom pain relief from medication) and 25, 26 (residual limb pain relief from medication), respectively.

2.10. Sample size considerations

Our sample size estimate was based on the primary specific aim of whether the addition of an ambulatory continuous peripheral nerve block decreases phantom limb pain intensity compared with placebo at 4 weeks after the initial catheter insertion and randomization. Receiver operating characteristic curve analyses demonstrate that changes from baseline of at least 1.7 along a 10-point NRS accurately identified participants who rated improvements as "much improved" or more, compared with those who perceived no change or worsening after analgesic interventions.[18] Multiple additional studies confirm this degree of reduction as clinically meaningful to individual patients with chronic pain.[14,17,20] Of note, meaningful group differences in the mean change would be somewhat smaller than important changes for individuals.[13]

The study was powered to be able to detect group differences in mean change from baseline of 1.7 points or more on the NRS. Based on a conservative SD estimate for each group of 3.0 at 4 weeks, a correlation of 0.50 between baseline and follow-up NRS, a two-sided test at the 0.05 significance level, power of 0.90, and 4 equally spaced analyses (3 interim and 1 final, as needed; Supplemental Figure B, available at http://links.lww.com/PAIN/B196), a maximum of 72 participants in each group (n = 144 total) was required (East 5.3 software; Cytel Inc). The expected sample size for this group sequential design (ie, average sample size over thousands of such trials, stopping when a boundary is crossed) was a total of 100 under the alternative and 102 under the null hypotheses. Boundary crossing probabilities at each of the 4 analyses for this design (Supplemental Table A, available at http://links.lww.com/PAIN/B196), assuming that either the null or alternative hypotheses were true.

3. Results

Between December 2013 and October 2018, a total of 144 patients were enrolled (**Fig. 1**). For both study groups, phantom limb pain fell from a median (interquartile range) of 5.0 (3.0, 7.0) immediately before the initial single-injection lidocaine bolus to 0 (0, 2.0) 20 minutes after the bolus. Residual limb pain similarly fell to 0 (0, 0) for all participants (**Table 1**). Patients were subsequently randomized to either active treatment with a ropivacaine (n = 71) or normal saline placebo (n = 73) 6-day infusion. Of baseline characteristics (**Table 1**), only pain's interference with sleep was imbalanced between the 2 randomized groups with an absolute standardized difference of 0.36 (>imbalance criterion of 0.33) and was adjusted for in the analysis of the primary outcome. One patient began her infusion but withdrew from the study on the day after catheter insertion and was included in all analyses per the intent-to-treat protocol.

3.1. Primary outcome

Pretreatment average phantom pain scores were balanced between randomized groups, with a median (interquartile range) of 5.0 (4.0, 7.0) for each. After 4 weeks (3 weeks after treatment ended), average phantom limb pain intensity was a mean (SD) of 3.0 (2.9) in patients given local anesthetic vs 4.5 (2.6) in those given placebo (difference [95% CI] 1.3 [0.4, 2.2], $P = 0.003$). The change from baseline was similar with pain severity decreasing by a mean (SD) of 2.4 (3.0) points in patients given local anesthetic vs 0.9 (2.3) points in those given placebo (difference [95% CI] 1.4 (0.5, 2.4), $P = 0.002$; **Table 2**).

At this same time point, average phantom pain severity was a mean (SD) of 3.0 (2.9) for active treatment and 4.5 (2.6) for patients who had received placebo, with an estimated difference in means (95% CI) of −1.3 (−2.2, −0.4) using last-observation-carried-forward; $P = 0.003$, **Table 2** and **Figure 2**). Nearly identical results were obtained using multiple imputation ($P = 0.002$, not shown). The nonparametric Hodges–Lehmann estimator gave a very similar result as well, with median difference (95% CI) of −1 (−3, 0), $P = 0.013$ (not shown).

3.2. Secondary outcomes at 4 weeks

Using the 1 to 7 Global Impression of Change Scale, subjects who had received active treatment rated their phantom pain as a median of 5 ("improved")[4,7] vs 4 ("no change")[4,5] for placebo subjects with an estimated median difference (95% CI) of 0 (0, 1), $P = 0.008$ (aim 2A) (**Table 2**). Similarly, subjects who had

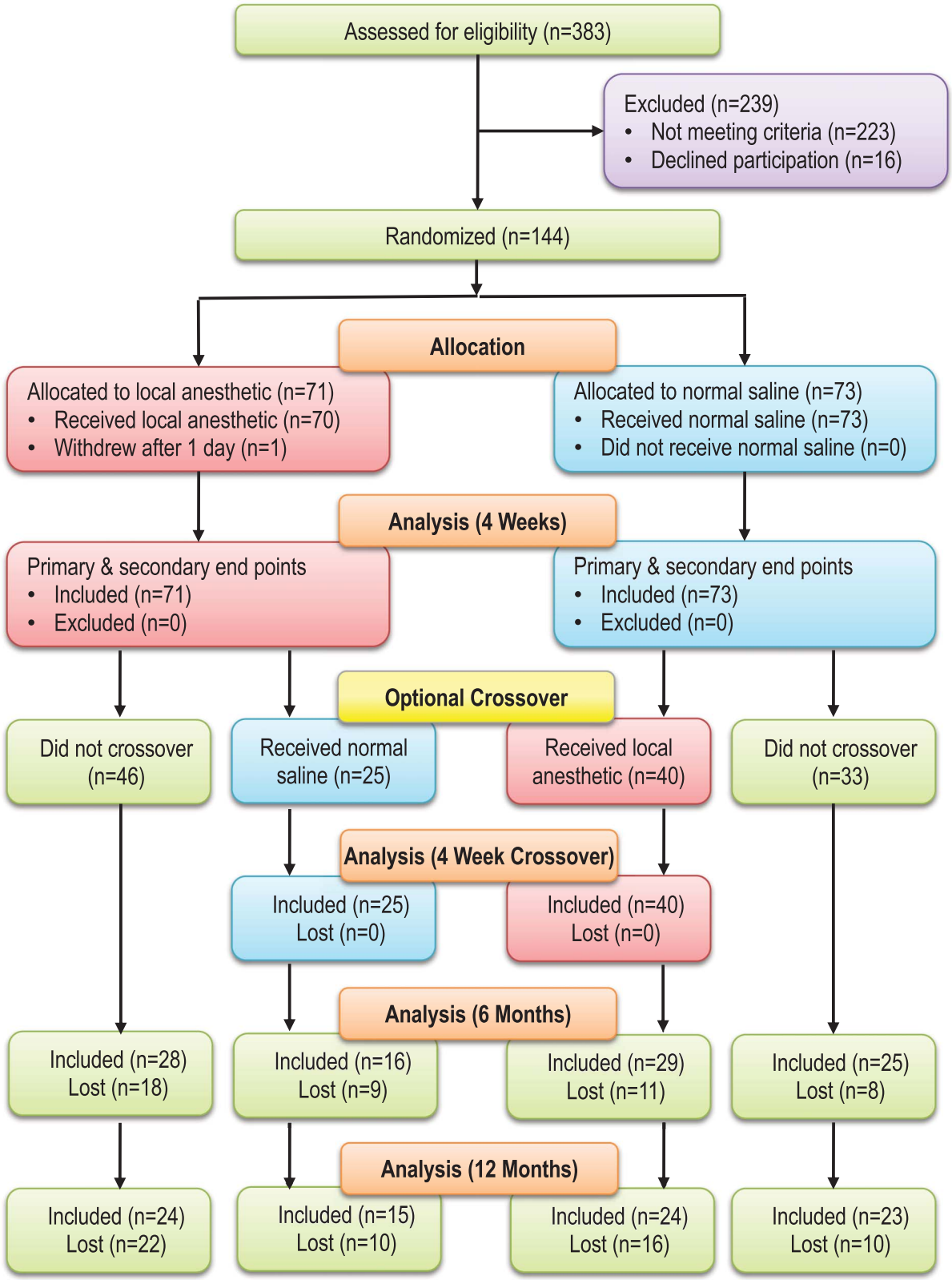

Figure 1. CONSORT diagram.

received active treatment had less pain-induced physical and emotional dysfunction, with a median Brief Pain Inventory interference subscale of 11 (0, 38) vs 28,[4,45] median difference (95% CI) of −6 (−17, 0), $P = 0.027$ (aim 2B, **Fig. 3**). The mixed-effects model suggested no treatment-by-component interaction ($P = 0.64$), with difference in means (CI) (scale 0-10) of −1.19 (−1.2, −0.4), $P = 0.003$. No difference was found on the BDI (aim 2C), with subjects receiving active treatment reporting a median of 6[2,17] vs 13[4,22] for placebo (difference [CI] of −2 [−6, 2]; $P = 0.299$).

Table 2

Effects of treatment group on primary and secondary outcomes at the 4-week time point (n = 144).

	Active (N = 71)	Placebo (N = 73)	Difference in means*†‡ or medians§ R-S (95% CI)‖	*P*
Primary outcome				
Average phantom limb pain intensity	3.0 ± 2.9	4.5 ± 2.6	−1.3 (−2.2, −0.4)*	0.003
Change from baseline	−2.4 ± 3.0	−0.9 ± 2.3	−1.4 (−2.4, −0.5)†	0.002
Secondary outcomes				
Global impression of change	5.0 [4.0, 7.0]	4.0 [4.0, 5.0]	0 (0, 1.0)§	0.008
Pain-related interference¶				
Total of 7 components	11 [0, 38]	28 [4, 45]	−6 (−17, 0)§	0.027
Treatment–component interaction				0.643
Overall treatment effect	3.1 (0.3)	4.3 (0.3)	−1.2 (−1.2, −0.4)‡	0.003
Individual components				
General activity	1.0 [0, 6.0]	5.0 [0, 7.0]	0 (−2, 0)§	0.122
Mood	0 [0, 6.0]	5.0 [0, 8.0]	−1 (−3, 0)§	0.014
Walking ability	0 [0, 3.0]	3.0 [0, 7.0]	0 (−2, 0)§	0.023
Normal work	0 [0, 6.0]	3.0 [0, 6.0]	0 (−2, 0)§	0.060
Relations with others	0 [0, 5.0]	2.5 [0, 6.5]	0 (−2, 0)§	0.045
Sleep	2.5 [0, 8.0]	5.5 [1.0, 8.0]	0 (−2, 0)§	0.190
Enjoyment of life	1.0 [0, 7.0]	4.0 [0, 7.0]	0 (−2, 0)§	0.152
Beck depression inventory				
Total	6 [2, 17]	13 [4, 22]	−2 (−5, 2)§	0.299
Minimal depression	32 (56%)	28 (44%)		
Mild depression	11 (19%)	15 (23%)		
Moderate depression	11 (19%)	14 (22%)		
Severe depression	3 (5%)	7 (11%)		
Tertiary outcomes				
Phantom limb pain				
Worst	5.0 [1.0, 8.0]	8.0 [5.5, 9.0]	−2 (−3, 0)§	0.004
Least	0 [0, 3.0]	2.0 [0, 4.0]	0 (−1, 0)§	0.074
Current	0.5 [0, 4.0]	4.0 [0, 7.0]	−1 (−3, 0)§	0.020
Total#	11 [1, 21]	18 [11, 27]	−6 (−10, −1)§	0.006
Residual limb pain				
Worst	0 [0, 5.0]	6.0 [0, 8.0]	−1 (−4, 0)§	0.007
Average	0 [0, 2.5]	3.0 [0, 5.0]	−1 (−2, 0)§	0.006
Least	0 [0, 0.5]	0 [0, 3.0]	0 (0, 0)§	0.051
Current	0 [0, 1.0]	1.0 [0, 5.0]	0 (−1, 0)§	0.034
Total#	0 [0, 9]	9 [0, 21]	−4 (−8, 0)§	0.007
Blinding assessment (fluid received from participants' perspective)				
Definitely active	10 (14%)	2 (3%)		
Probably active	17 (24%)	8 (11%)		
Does not know	18 (25%)	18 (25%)		
Probably placebo	16 (23%)	33 (45%)		
Definitely placebo	3 (4%)	4 (5%)		

Data for each group reported as mean (SD), median [interquartile range], or number (percentage).
The summary statistics were reported with complete data, and all analyses were based on all 144 patients with 5 imputed data sets.
Number of missing values for ropivacaine 0.5% and saline groups are: 14 and 9 for Beck depression inventory, 5 and 4 for Global impression of change, 7 and 8 for blinding assessment, 5 and 3 for all other variables, respectively.
* Difference in means for 2 groups was estimated from a multivariable linear regression model adjusting for baseline average pain intensity, site, and baseline sleep, using last-observation-carried-forward method.
† Difference in means for 2 groups was estimated from a multivariable linear regression model adjusting for baseline average pain intensity, site, and baseline sleep, using imputed data sets.
‡ Overall treatment effect: Difference in means between 2 groups across the 7 components was estimated from a linear mixed-effects regression model. The model adjusted for study site, baseline pain interference components. Treatment by component interaction was nonsignificant ($P = 0.64$). Per-group mean (SE) across components is also reported.
§ Difference in medians of 2 groups was estimated from Wilcoxon rank sum test and the Hodges–Lehmann estimator of location shift between groups, stratified by study sites.
‖ Confidence intervals adjusted for group sequential design to maintain overall study alpha of 0.05. *P* value of 0.044 or less was considered significant for treatment effect on all outcomes.
¶ *P* values of 0.006 (0.044/7, Bonferroni correction) were considered significant for individual components.
# Total scores for phantom/residual limb pain are the sum of worst, least, average, and current pain of phantom/residual limb, respectively, with possible range of 0 to 40.

As described in Methods, type I error was controlled at 5% across the above primary and secondary outcomes using parallel gatekeeping. Using that approach, the significance criterion for each test remained at the nominal 0.044 (adjusting for interim monitoring) because each of the first 3 (out of 4) sequential tests was statistically significant.

3.2.1. Subgroup analyses

There was little evidence of treatment effect heterogeneity across levels of most of the selected baseline (prerandomization) variables, except for amputation side of study limb (interaction $P = 0.057$, **Fig. 4**). Treatment effect also did not differ by etiology (traumatic vs surgical amputation, $P = 0.567$ [not displayed]). Significant interaction was claimed if P value < 0.10.

3.3. Tertiary outcomes

Ropivacaine significantly improved other 4-week phantom and residual limb pain outcomes (**Table 2** and **Figs. 2 and 5**). The crossover treatment administered 0 to 12 weeks after the measurement of the primary outcome was optional, resulting in

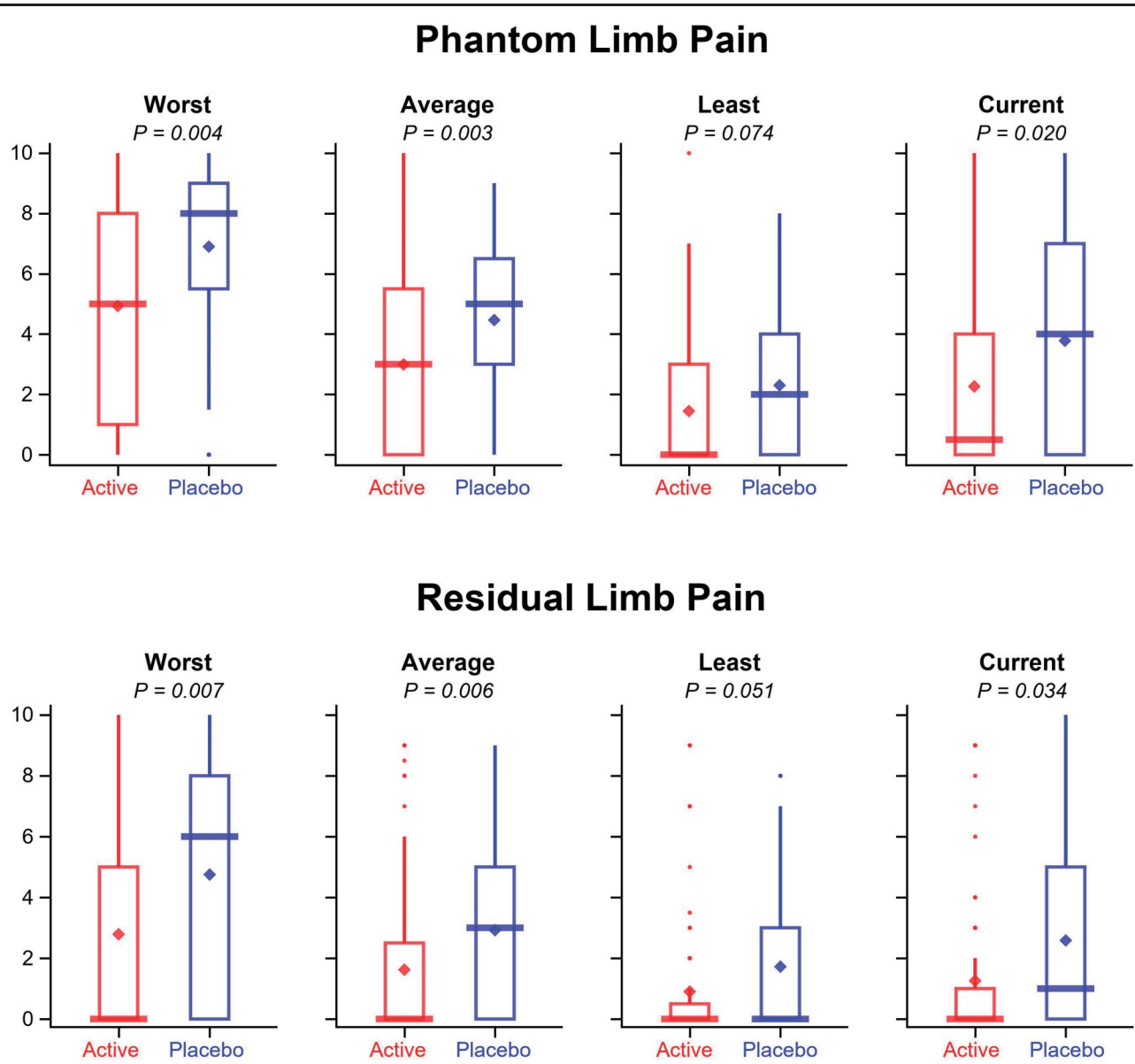

Figure 2. Effects of a 6-day continuous peripheral nerve block on *phantom* and *residual* limb pain at the primary outcome time point of 4 weeks (primary outcome: *average* phantom limb pain). Pain severity indicated using a numeric rating scale of 0 to 10, with 0 equal to no pain and 10 being the worst imaginable pain. Data expressed as median (dark horizontal bars) with 25th to 75th (box), 10th to 90th (whiskers), mean (diamonds), and outliers (circles).

selection bias on patients who did not cross over, and potential interference with the longer-term effects of the initial treatment on those who did cross over. Therefore, outcomes after the 4-week time point are reported descriptively only.

3.4. Crossover treatment effect

For the n = 65 patients who participated in the crossover phase, the baseline characteristics were compared between patients whose initial randomization was active (n = 25) vs placebo (n = 40) in **Table 3**. The crossover treatment effect on all outcomes is reported in **Table 4**. Active treatment was significantly better than placebo on 28-day phantom limb pain intensity, with an estimated within-patient mean difference of −0.94 (95% CI: −1.61, −0.27; $P = 0.007$). The period by treatment interaction *P*-value of 0.87 suggests that there was no evidence of differential carryover effect. Significant reductions were also found for the pain interference total score and the PGIC score (**Table 4**). These results are generalizable to patients like those who chose to receive the crossover, which may differ from the main trial population.

As well, active treatment had a larger reduction from baseline in average phantom limb pain intensity with a mean (95% CI) of −1.45 (−2.3, −0.63), $P < 0.001$. The variability in the individual causal effects of active vs placebo as measured by the SD of the individual treatment effects was 2.7.

3.5. Outcomes at 6 and 12 months postrandomization

The crossover treatment administered 0 to 2 weeks after the measurement of the primary end point was optional, resulting in selection bias on patients who did not cross over, and potential interference with the long-term effects of the initial treatment on those who did cross over. Therefore, 6- and 12-month results comparing initial active and placebo assignment by crossover status are reported descriptively only (**Tables 5 and 6**).

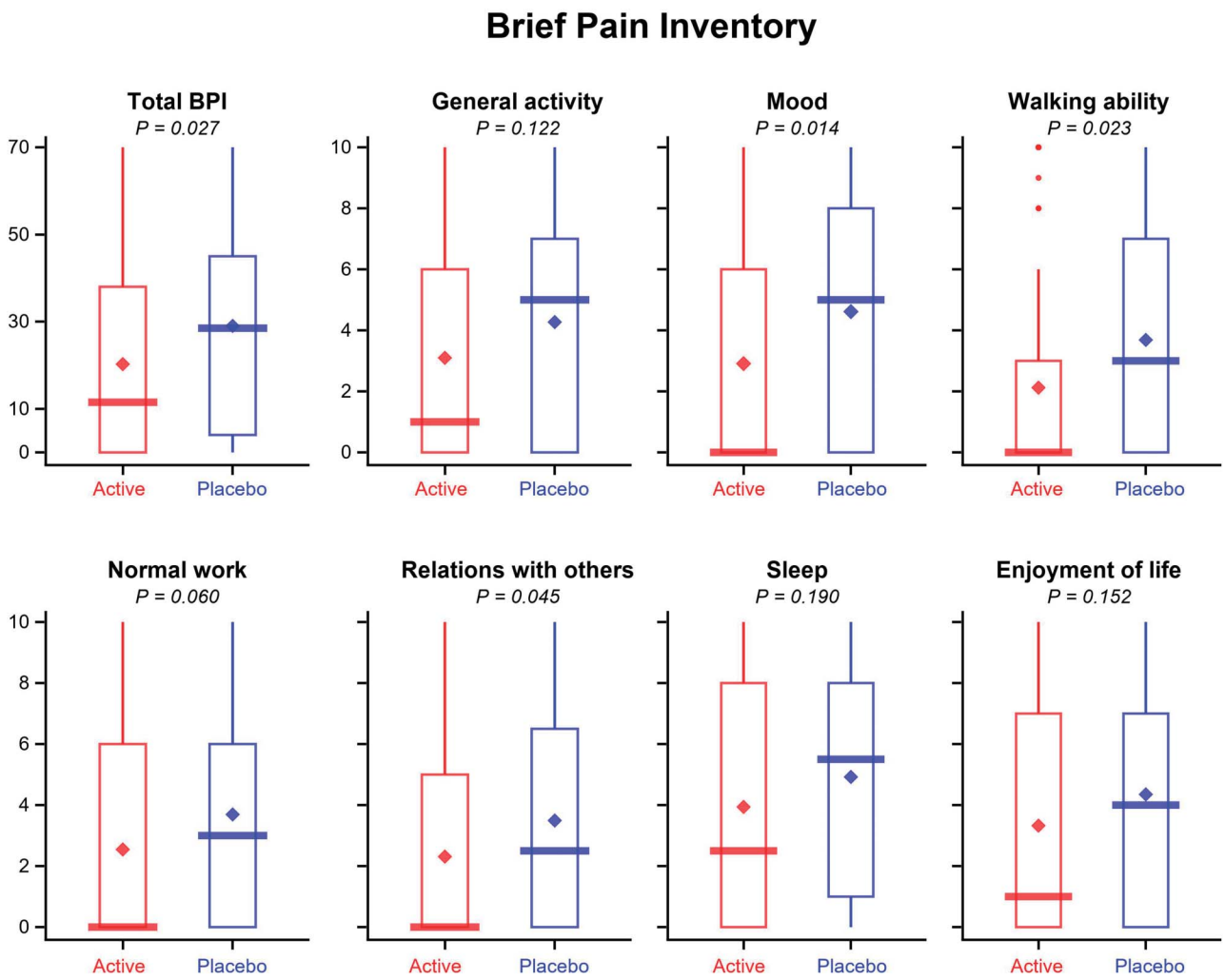

Figure 3. Effects of a 6-day continuous peripheral nerve block on the *Brief Pain Inventory* (BPI) interference domain at 4 weeks. Total score was 1 of 3 secondary outcomes, whereas the individual components were tertiary outcomes. Data expressed as pain's interference on each component (higher scores = more interference) demarked as median (dark horizontal bars) with 25th to 75th (box), 10th to 90th (whiskers), mean (diamonds), and outliers (circles).

3.6. Assessment of blinding

For assessment of the blinding, the distribution of participants' responses is shown in **Table 2**; n = 15 participants did not answer the question and were not included in the blinding assessment. James' BI (95% CI) was 0.50 (0.42, 0.59), implying a result halfway between blinded and unblinded. However, from the Bang BI, we conclude that the treatment group was quite well blinded, with estimate (95% CI) of 0.13 (−0.05, 0.30), which overlaps 0 (blinded), whereas the control group had a Bang BI of 0.42 (0.26, 0.57), halfway between blinded and unblinded. So, the average control patient was more likely to know what they received compared to the average treated patient. This is not surprising in a treatment that is working in many patients.

3.7. Adverse events

Based on patient report, 8 catheter sites showed signs of possible localized infection out of 382 total catheters (2.1%): 2 on day 2, and 6 on days 5 to 7. Three patients received oral antibiotics, and all symptoms resolved within 2 days after catheter removal. There was one serious adverse event among 382 catheters (0.3%): one patient reported increased phantom pain beginning 2 days after catheter insertion and infusion initiation after returning home to a different state than his treatment center.[31] At a local emergency department, a physician withdrew both femoral and sciatic catheters, the increased pain resolved, and the patient was without complaints until he presented 5 months later with a discharging sinus at the sciatic catheter insertion site. A retained piece of the catheter was subsequently removed, the patient placed on antibiotics, and his infection healed without further incident.

4. Discussion

A 6-day ambulatory perineural local anesthetic infusion substantially decreased phantom limb pain 4 weeks after the initiation of treatment with average intensity a mean (SD) of 3.0 (2.9) in patients given the active treatment vs 4.5 (2.6) in those given placebo (P = 0.003). Residual limb pain was decreased to an even greater extent with average intensity a median (interquartile) of 0 (0, 2.5) vs 3.0 (0, 5.0) for the active and placebo groups, respectively (P = 0.006). Correspondingly, patients' global impression of change improved and pain-related life interference decreased by clinically important amounts.[14] Depression also decreased by a clinically meaningful amount (≥5 points as defined by IMMPACT consensus guidelines),[14] although the difference was not statistically significant.

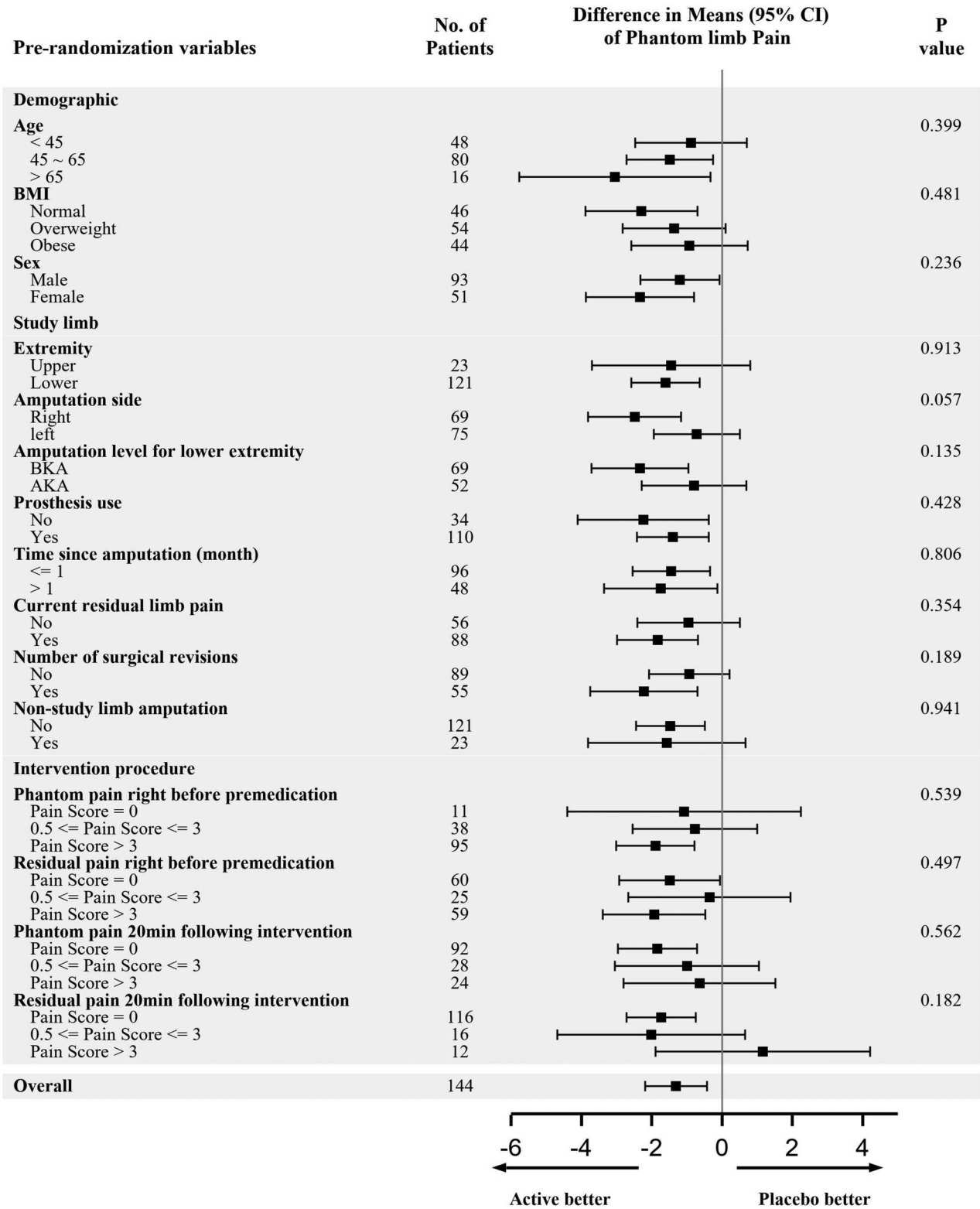

Figure 4. Forest plot assessing interactions between prespecified baseline factors and the effect of a 6-day continuous peripheral nerve block on phantom limb pain.

Relatively brief ambulatory local anesthetic infusions thus produced substantial and prolonged benefit in patients with phantom limb pain. This nonopioid treatment carries significant public health impact, given the millions of affected individuals, especially considering this pain can be notoriously difficult to treat and the extent to which it impairs quality of life and productivity. In addition, although the study protocol does not permit conclusions regarding the precise etiology of phantom pain, the results provide strong evidence that phantom pain is often maintained from abnormal peripheral input.[21,23]

Because of the optional crossover design mandated by the funding agency, it is difficult to estimate treatment-effect duration

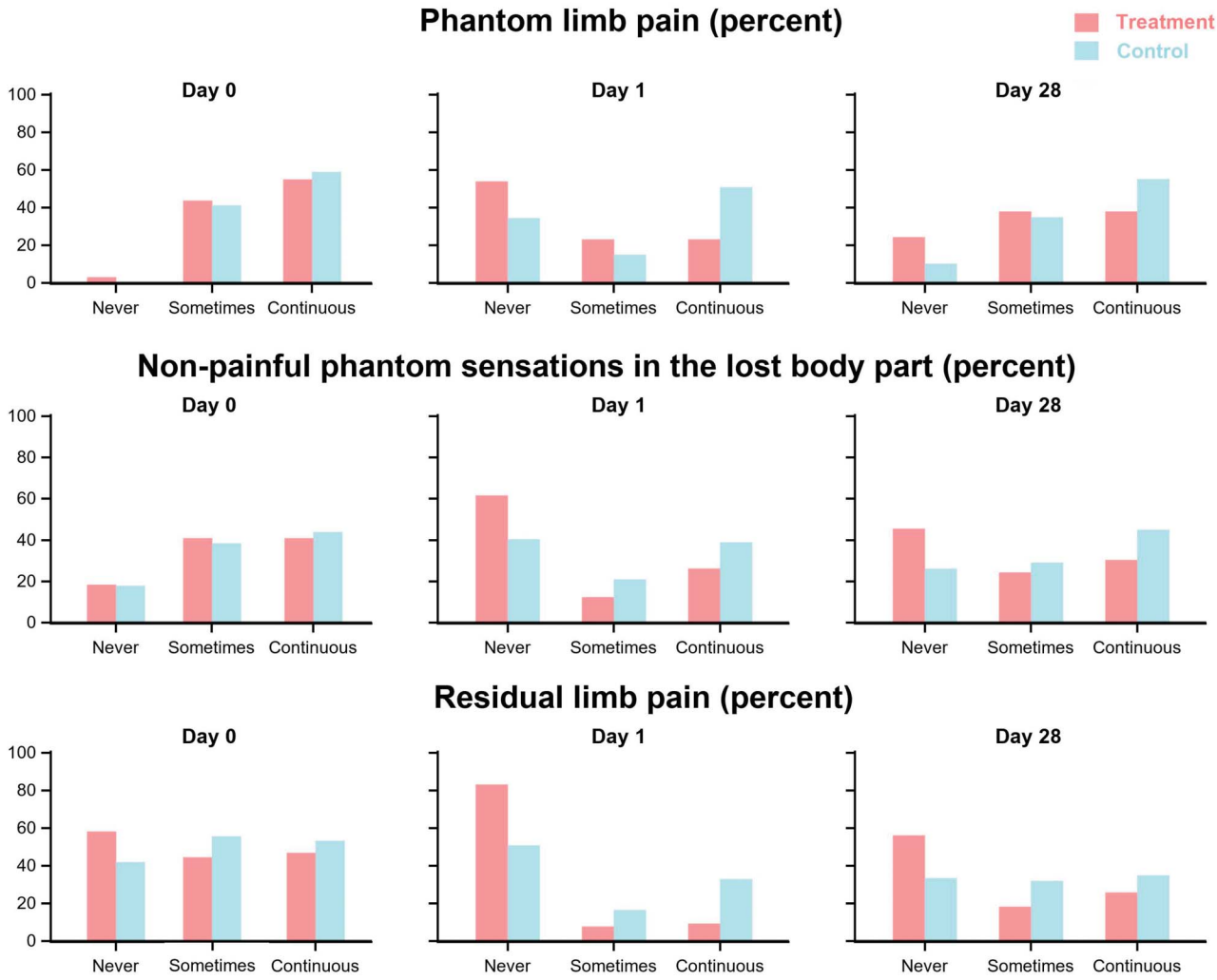

Figure 5. Effects of a 6-day continuous peripheral nerve block on the *incidence* of phantom limb pain, nonpainful phantom sensations, and residual limb pain, at baseline (day 0), during the perineural infusion (day 1) and 4 weeks after the initiation of the treatment. Data expressed as a percentage of the treatment group.

beyond 4 weeks due to selection bias. But restricting analysis to the substantial number of patients who did not receive a self-selected crossover treatment, we can estimate benefit at 6 and 12 months with the understanding that the results do represent a biased sample (ie, subjects selected to not receive the crossover, for whatever reason). The median change in *phantom* limb pain at 6 months for the treated patients was −3.0 (−5.0, 0) vs −1.5 (−5.0, 0) for the placebo group, whereas there was little apparent residual benefit for *phantom* pain at 12 months. It is also notable that after 12 months, average *residual* limb pain for the treatment group remained decreased by a median of 2.0 (0, 4.0) on the NRS vs no change (0, 3.5) for the control group.

The remaining participants who chose to undergo the elective crossover treatment presumably did so due to a perceived inadequate response to their initial infusion. It is noteworthy that subjects who received active treatment during the crossover reported far less improvement compared with those who received local anesthetic during their initial infusion. This may be evidence that the single-injection local anesthetic block that all participants initially received benefitted a subset of patients[5]; and, it was this group that self-selected to forgo crossover, leaving the remaining participants who were not as responsive to the local anesthetic infusion regardless of the timing either during the initial or crossover infusion.

About 2% of our patients reported signs of catheter-related infections. Most investigations report an infection rate of less than 1% for infusions up to 4 days and 4% after 1 week.[6,26] Within our study, only 2 (0.5%) possible infections occurred within the first 4 days and 7 (2.1%) at 6 days, and thus our incidence was lower than the majority of published series.[6,26] It is worth considering, though, that continuous perineural catheters are most commonly used perioperatively, a period during which nearly all patients are given prophylactic antibiotics. By contrast, our patients did not receive prophylactic antibiotics, making the relatively low infection rate reassuring.[7] Although any infection is concerning, there are no reports of permanent disability due to an infected perineural catheter. Treatment usually consists of catheter removal and oral antibiotics.[26]

Although catheters were inserted under ultrasound guidance, all subjects received an initial bolus of intermediate-acting local anesthetic through the catheter before receiving their randomized treatment. Therefore, even subjects who subsequently received the saline placebo had a single-injection peripheral nerve block. We chose this protocol for 2 reasons. First, although ultrasound guidance is now the overwhelmingly favored technique for catheter insertion due to ease and speed of placement,[26] fine fascial layers often cannot be visualized and the exact location of catheter placement with regards to fascial layers is hard to determine.

Table 3

Crossover baseline characteristics (N = 65).

Initial treatment:	Active (n = 25)	Placebo (n = 40)
Demographics		
Age (y)	48 ± 16	49 ± 14
Female (%)	6 (24)	17 (43)
Body mass index (kg/m^2)	27 [22, 30]	27 [23, 32]
Marital status (%)		
Single (or divorced)	10 (40)	22 (55)
Currently married	15 (60)	12 (30)
Others (separated and widowed)	0 (0)	6 (15)
Military status (%)†		
Civilian (never in military)	21 (84)	33 (83)
Veteran	4 (16)	7 (18)
Years of education	14 [13, 16]	14 [12, 16]
Amputation information†		
Lower extremity (%)	19 (76)	33 (83)
Above knee	14 (74)	13 (39)
Below knee	5 (26)	20 (61)
Upper extremity (%)	6 (24)	7 (18)
Above elbow	5 (83)	5 (71)
Below elbow	1 (17)	2 (29)
Right (v. Left) side (%)	7 (28)	20 (50)
History of residual limb pain (%)	15 (60)	35 (88)
Current residual limb pain (%)	13 (52)	32 (80)
Current prosthesis use (%)	19 (76)	31 (78)
Additional limb amputation(s) (%)	5 (20)	5 (13)
Phantom pain previous 3 d (numeric rating scale)		
Current	4.0 [3.0, 6.0]	6.0 [4.0, 7.5]
Least	2.0 [0, 5.0]	5.0 [2.0, 6.0]
Average	6.0 [3.0, 7.0]	6.0 [5.0, 7.0]
Worst	7.0 [5.0, 10]	8.0 [8.0, 9.0]
Residual limb pain previous 3 d (numeric rating scale)		
Current	1.0 [0, 3.0]	3.0 [0, 6.0]
Least	0 [0, 3.0]	2.0 [0, 5.0]
Average	1.0 [0, 5.0]	5.0 [1.5, 6.0]
Worst	2.0 [0, 7.0]	7.5 [2.5, 8.0]
Phantom pain relief from medication (%)*		
0%-25%	9 (36)	10 (25)
26%-50%	7 (28)	12 (30)
51%-75%	1 (4)	6 (15)
76%-100%	4 (16)	2 (5)
Residual limb pain relief from medication (%)*		
0%-25%	7 (28)	9 (23)
26%-50%	4 (16)	12 (30)
51%-75%	2 (11)	4 (10)
76%-100%	2 (11)	2 (5)
Pain interference components		
General activity	4.0 [2.0, 9.0]	5.0 [1.5, 7.0]
Mood	5.0 [3.0, 8.0]	5.0 [2.5, 7.5]
Walking ability	2.0 [0, 10]	4.0 [0, 7.5]
Normal work	3.0 [0, 8.0]	6.0 [2.0, 8.0]
Relations with other people	3.0 [0, 6.0]	4.0 [0, 6.5]
Sleep	4.0 [0, 6.0]	6.5 [3.0, 8.0]
Enjoyment of life	4.0 [2.0, 7.0]	4.0 [2.5, 7.0]
Depression		
Beck depression inventory	9 [5, 18]	13 [8.0, 23]
Beck depression category (%)		
Minimal	14 (56)	15 (38)
Mild	5 (20)	11 (28)
Moderate	4 (16)	9 (23)
Severe	2 (8)	5 (13)
Pain immediately before and after initial local anesthetic bolus		

(*continued on next page*)

Table 3 (*continued*)

Initial treatment:	Active (n = 25)	Placebo (n = 40)
Phantom pain		
Immediately before	4.0 [3.0, 6.0]	6.0 [3.5, 7.0]
20 minutes after	0 [0, 2.0]	0 [0, 2.0]
Residual limb pain		
Immediately before	0 [0, 3.0]	3.5 [0, 6.0]
20 minutes after	0 [0, 0]	0 [0, 0.5]

* Number of missing values for active and control group are 4, 10 (Phantom limb pain relief from medication) and 10, 13 (residual limb pain relief from medication), respectively.
†Totals not equal to 100% due to rounding error.

Therefore, initially administering a local anesthetic bolus through the catheter and ensuring appropriate sensory deficits within 20 minutes demonstrated accurate catheter insertion. Second, we wanted to confirm that perineural local anesthetic would not induce paradoxical pain, a rare response (which we did not observe after the single injections of local anesthetic).[39]

Our instructions to participants included the information that any sensory changes they experienced with catheter insertion would frequently resolve after 4 to 8 hours, so that participants would not think there was a catheter or pump problem upon lidocaine resolution. This instruction probably helped retain treatment assignment masking: at the 28-day primary outcome time point, only 14% of the active and 5% of the placebo groups accurately replied they "definitely" received their assigned treatment. For the crossover infusion, only 8% of participants who had received active treatment believed they had "probably" or "definitely" received local anesthetic; and only 24% of participants who had received placebo accurately guessed their treatment group.

Deserving comment is the potential for widespread application of ambulatory continuous peripheral nerve blocks to treat phantom limb pain. Unlike epidural injection/infusion,[22] many healthcare providers treating chronic pain are unfamiliar with continuous peripheral nerve blocks because they are generally used to treat acute postoperative pain.[9,26] However, ambulatory continuous peripheral nerve blocks have significant benefits compared with epidurals, which make them far more likely to be implemented in treating established phantom pain: they may be provided on an ambulatory basis avoiding the expense, patient inconvenience, and logistical challenge of a hospital stay; effect

Table 4

Four-week time point after the *crossover* treatment (n = 65).

	Active (n = 65)	Placebo (n = 65)
Phantom pain previous 3 d (numeric rating scale)		
Current	2.5 [0.0, 5.0]	5.0 [2.5, 8.0]
Least	0 [0.0, 3.5]	3.0 [1.0, 5.0]
Average	4.0 [1.0, 6.0]	5.0 [4.0, 7.0]
Worst	7.0 [3.0, 9.0]	8.0 [7.0, 10]
Residual limb pain previous 3 d (numeric rating scale)		
Current	0 [0, 4.0]	2.0 [0, 6.0]
Least	0 [0, 2.0]	0 [0, 3.0]
Average	1.0 [0, 4.5]	3.0 [0, 6.0]
Worst	3.0 [0, 8.0]	6.0 [0, 8.0]
Pain interference		
Total score	16 [2, 42]	38 [16, 50]
General activity	3.0 [0, 6.0]	6.0 [3.0, 8.0]
Mood	3.0 [0, 6.0]	6.0 [2.0, 8.0]
Walking ability	0 [0, 6.0]	3.0 [0, 8.0]
Normal work	1.5 [0, 6.0]	4.0 [0, 8.0]
Relations with others	1.0 [0, 4.0]	4.0 [0, 8.0]
Sleep	4.0 [0, 8.0]	6.0 [3.0, 9.0]
Enjoyment of life	2.0 [0, 7.0]	5.0 [1.0, 8.0]
Global impression of change	4.0 [4.0, 7.0]	4.0 [4.0, 5.0]
Depression (Beck depression inventory)		
Total	8.0 [2.0, 19]	15 [4.0, 22]
Minimal	30 (53)	21 (39)
Mild	12 (21)	12 (22)
Moderate	12 (21)	17 (32)
Severe	3 (5)	4 (7)

Within-patient results for the N = 65 patients who crossed over at 4 week and thus received both Active (first column) and Placebo (second column) either initially or later. The 2 columns ignore which treatment was received first. Number of missing are 8 and 11 for Beck Pain Inventory in Active and Placebo group, respectively, 3 for Global Impression of Change and 2 for all other variables for both groups.
Active and placebo refer to the treatments that each of these 65 patients received, either initially or in crossover. Analysis adjusted for the ordering. Table summary statistics ignore the within-patient ordering for easier viewing of the crossover treatment effect.
Difference in means of active vs placebo was estimated using a mixed-effects regression model with a fixed effect for treatment and a compound symmetry correlation matrix. The model adjusted for treatment sequence and period.
Difference in medians of active vs placebo was estimated from Wilcoxon rank sum test and the Hodges–Lehmann estimator of location shift between groups, stratified by treatment sequence and period.

Table 5

Long-term follow-up at 6 months postrandomization.

Initial Treatment:	Active	Placebo	Active	Placebo
	No crossover		Had crossover	
	(n = 46)	(n = 33)	(n = 25)	(n = 40)
Phantom pain				
Worst pain	−2.0 [−6.0, 0]	−2.5 [−5.0, 0]	0 [−2.0, 1.0]	−1.0 [−3.0, 0]
Average pain	−3.0 [−5.0, 0]	−1.5 [−5.0, 0]	0 [−1.8, 1.0]	−1.0 [−3.5, 0]
Residual limb pain				
Worst pain	−1.0 [−5.0, 0]	0 [−4.0, 0]	0 [−0.5, 0]	0 [−2.0, 1.0]
Average pain	−1.0 [−3.0, 0]	0 [−2.0, 0]	0 [−0.25, 0]	−1.0 [−2.0, 0]
Brief pain inventory components				
General activity	−1.5 [−6.0, 0]	−2.0 [−5.0, 1.0]	0 [−1.5, 1.0]	−2.0 [−5.0, 0]
Mood	−1.0 [−5.0, 0]	−1.0 [−4.0, 0]	0 [−2.0, 1.0]	−1.0 [−5.0, 0]
Walking ability	0 [−7.0, 0]	−1.0 [−5.0, 0]	0 [−1.0, 0]	−1.0 [−3.0, 0]
Normal work	−2.5 [−6.5, 0]	−1.0 [−5.0, 0]	0 [−1.5, 1.0]	−1.0 [−6.0, 0]
Relations with others	−1.0 [−5.5, 0]	0 [−5.0, 0]	0 [−1.5, 1.0]	0 [−3.0, 1.0]
Sleep	−3.8 [−7.0, 0]	−1.5 [−6.0, 0]	0 [−1.0, 0]	−1.0 [−6.0, 0]
Enjoyment of life	−2.0 [−7.5, 0]	−1.0 [−5.0, 0]	0 [−2.0, 0]	−2.0 [−5.0, 0]
Global impression change	7.0 [4.0, 7.0]	5.0 [4.0, 7.0]	4.0 [4.0, 5.0]	4.0 [4.0, 7.0]
Beck depression inventory	−3 [−11, 0]	−2 [−6, 0]	−1.5 [−2, 0]	−4 [−8, 0]

Values represent the change from initial baseline with the exception of the Patient Global Impression of Change, which are presented as raw values (n = 144).
Data presented as median [interquartile range].
Number of missing values for the Beck Depression Inventory are 20, 11, 11, and 17, and for other variables are 18, 8, 9, and 11 for the groups, starting from the left, respectively.

exclusively the targeted limb allowing ambulation with crutches (unlike an epidural with bilateral effects); usually provide a denser block; can treat upper-extremity in addition to lower-extremity amputations; and have essentially no systemic side effects such as hypotension and urinary retention.[26] Furthermore, perineural catheter insertion is routinely taught in anesthesiology training programs and usually requires less than 15 minutes per catheter; and, portable ultrasound machines used for catheter insertion are now ubiquitous in medical facilities. These characteristics result in a relatively low cost and allow perineural infusion to be administered even in austere environments,[36] increasing the possibility of widespread application, including locations without advanced healthcare facilities.

4.1. Comparison to other studies

Our results involving peripheral nerve blocks build on the work of previous investigators. Birbaumer and colleagues demonstrated that a single-injection peripheral nerve block in the amputated limb can result in resolution of both the cortical abnormalities and

Table 6

Long-term follow-up at 12 months postrandomization.

Initial treatment	Active	Placebo	Active	Placebo
	No crossover		Had crossover	
	(n = 46)	(n = 33)	(n = 25)	(n = 40)
Phantom pain				
Worst pain	−2.0 [−4.0, 0]	−1.0 [−5.0, 0]	0 [−2.0, 1.0]	−1.5 [−3.3, 0]
Average pain	−2.5 [−4.0, −0.5]	−2.0 [−5.0, 0]	−1.0 [−4.0, 0]	−1.0 [−3.0, 0]
Residual limb pain				
Worst pain	−3.0 [−7.0, 0]	0 [−1.0, 0]	0 [−1.0, 0]	0 [−2.0, 1.0]
Average pain	−2.0 [−4.0, 0]	0 [−3.5, 0]	0 [−2.0, 0]	−1.0 [−1.5, 0]
Brief pain inventory components				
General activity	−1.0 [−4.0, 0]	−1.0 [−5.0, 0]	−1.0 [−4.0, 1.0]	−1.0 [−3.5, 0]
Mood	0 [−4.0, 0]	−1.0 [−4.0, 0]	−1.0 [−4.0, 0]	−0.5 [−3.8, 1.0]
Walking ability	−1.0 [−6.0, 0]	0 [−5.0, 0]	0 [−3.0, 0]	0 [−4.5, 0]
Normal work	−1.0 [−5.0, 0]	−1.0 [−5.0, 0]	−3.0 [−6.0, 0]	−1.5 [−5.3, 0]
Relations with others	−1.0 [−2.0, 0]	0 [−3.0, 0]	−1.0 [−4.0, 0]	−0.5 [−4.0, 1.0]
Sleep	−1.0 [−6.0, 0]	0 [−6.0, 0]	−1.0 [−2.0, 0]	−0.5 [−6.5, 0.5]
Enjoyment of life	−1.0 [−5.0, 0]	−1.0 [−6.0, 1.0]	0 [−5.0, 0]	0 [−3.5, 1.0]
Global impression change	6.0 [4.0, 7.0]	5.0 [4.0, 7.0]	4.0 [4.0, 7.0]	4.0 [4.0, 7.0]
Beck depression inventory	−4 [−12, −1]	−2 [−9, 0]	−1.5 [−3, 0]	−4 [−9, −1]

Values represent the change from initial baseline with the exception of the Patient Global Impression of Change, which are presented as raw values (n = 144).
Data presented as median [interquartile range].
Number of missing values for the Beck Depression Inventory are 23, 12, 13, 18; for the Patient Global Impression of Change are 22, 10, 10, 16; and for other variables are 21, 10, 10, 16 for the groups, starting from the left, respectively.

phantom pain for the relatively short duration of the block.[5] Other clinical trials involving nerve blocks have involved attempts to *prevent* subsequent phantom limb pain development.[22,24] Borghi and colleagues treated a large series of patients undergoing lower-extremity surgical amputation with prolonged perioperative continuous peripheral nerve blocks in an attempt to decrease postoperative phantom limb pain, but without a control group the efficacy of the intervention remained undetermined.[9] Randomized controlled trials by Nikolajsen et al. as well as Lambert et al. found no improvement in postintervention phantom pain with a perioperative *epidural* local anesthetic infusion,[33,41,42] although one randomized study by Karanikolas and colleagues reported contrasting positive results.[29] The inconsistent outcomes of these studies are echoed by a host of others, and may be related to specifics of the intervention, particularly its time of initiation and duration.[30]

4.2. Limitations

A limitation of our trial relates to the optional crossover treatment after 4 to 6 weeks, thus introducing significant selection bias for data collected subsequent to the primary and secondary end points. Although the treatment effect certainly seemed to decrease over time, the actual duration remains unknown. However, because there is no limitation on repeating the catheter/infusion treatment,[26] patients could return for serial treatments if and when their pain returned, similar to epidural steroid injections for back pain.

Furthermore, the optimal infusion-related parameters are largely unknown, such as the ideal local anesthetic type, concentration, basal infusion rate, administration modality (eg, basal infusion vs repeated bolus doses), specific anatomic catheter location, and infusion duration.[26] It is likely that results would differ at least slightly were the infusion regimen different. But it also seems unlikely that our overall conclusions depend critically on minor protocol details. Our specific protocol was determined, in large part, by our inability to replenish participants' study fluid reservoir because many patients traveled long distances to one of our treatment facilities and returned home soon thereafter. However, this logistical issue was primarily an artifact of the clinical trial; and, for patients being treated locally who could more easily return to their treatment center/physician, perineural infusions of multiple months are feasible.[9]

In summary, a 6-day ambulatory continuous peripheral nerve block reduced phantom limb pain and pain-induced physical and emotional dysfunction 4 weeks after treatment, and often persisted for up to 6 months. Future research should investigate the optimal perineural infusion parameters and define the precise duration of analgesic benefits.

Conflict of interest statement

None of the authors has a personal financial interest in this research. B.M. Ilfeld and B. Khatibi: The University of California has received funding and product for other research projects from Myoscience (Fremont, CA), Epimed (Farmers Branch, TX), Infutronics (Natick, MA), Ferrosan Medical (Søborg, Denmark), SPR Therapeutics (Cleveland, OH), and Heron Therapeutics (San Diego, CA). J.C. Eisenach: Consulting to Adynxx (San Francisco, CA). The remaining authors have no conflicts of interest to declare.

A complete list of authors of the PAINfRE Investigators is provided in Appendix A, available at http://links.lww.com/PAIN/B196.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B196.

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