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Preoperative Ultrasound-guided Percutaneous Cryoneurolysis for the Treatment of Pain after Mastectomy: A Randomized, Participant- and Observer-masked, Sham-controlled Study

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ANESTHESIOLOGY 2022; 137:529–42

Scan for CME exam

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Percutaneous cryoneurolysis is a nonpharmacologic treatment used primarily for the control of chronic pain
- The ability of cryoneurolysis to control pain after breast surgery has not been evaluated

What This Article Tells Us That Is New

- A randomized trial design was used to compare analgesic requirements after breast surgery in those receiving paravertebral anesthetic blocks with those receiving the same blocks plus intercostal cryoneurolysis
- Patients receiving cryoneurolysis reported less pain on postoperative day 2, suggesting benefit of this treatment

ABSTRACT

Background: Ultrasound-guided percutaneous cryoneurolysis is an analgesic technique in which a percutaneous probe is used to reversibly ablate a peripheral nerve(s) using exceptionally low temperature, and has yet to be evaluated with randomized, controlled trials. Pain after mastectomy can be difficult to treat, and the authors hypothesized that the severity of surgically related pain would be lower on postoperative day 2 with the addition of cryoanalgesia compared with patients receiving solely standard-of-care treatment.

Methods: Preoperatively, participants at one enrolling center received a single injection of ropivacaine, 0.5%, paravertebral nerve block at T3 or T4, and perineural catheter. Participants subsequently underwent an active or sham ultrasound–guided percutaneous cryoneurolysis procedure of the ipsilateral T2 to T5 intercostal nerves in a randomized, patient- and observer-masked fashion. Participants all received a continuous paravertebral block with ropivacaine, 0.2%, until the early morning of discharge (usually postoperative day 2). The primary endpoint was the average pain level measured using a 0 to 10 numeric rating scale the afternoon of postoperative day 2. Participants were followed for 1 yr.

Results: On postoperative day 2, participants who had received active cryoneurolysis (n = 31) had a median [interquartile range] pain score of 0 [0 to 1.4] *versus* 3.0 [2.0 to 5.0] in patients given sham (n = 29): difference –2.5 (97.5% CI, –3.5 to –1.5), $P < 0.001$. There was evidence of superior analgesia through month 12. During the first 3 weeks, cryoneurolysis lowered cumulative opioid use by 98%, with the active group using 1.5 [0 to 14] mg of oxycodone compared with 72 [20 to 120] mg in the sham group ($P < 0.001$). No oral analgesics were required by any patient between months 1 and 12. After 1 yr chronic pain had developed in 1 (3%) active compared with 5 (17%) sham participants ($P < 0.001$).

Conclusions: Percutaneous cryoneurolysis markedly improved analgesia without systemic side effects or complications after mastectomy.

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Breast cancer is the most common malignancy in women, with more than 1,600,000 new cases and a half-million deaths identified annually worldwide.[1] Between 36 and 40% of patients diagnosed with breast cancer undergo mastectomy—approximately 100,000 annually in the United States alone—with these numbers increasing during the past 2 decades.[2,3] In addition, tens of thousands of women undergo prophylactic mastectomies due to either identified cancer in the contralateral breast or identification of genetic mutations (*e.g.*, BRCA1), both of

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which indicate an elevated cancer risk.[4,5] Pain in the acute postoperative period is frequently severe and can last for a month or more.[6]

Furthermore, mastectomy is one of the four surgical procedures at highest risk for transitioning from acute to persistent (chronic) pain,[7] with up to 57% of patients experiencing pain 6 to 12 months after surgery.[8] Inadequately controlled acute pain in the period after surgery is one of the greatest risk factors for the development of chronic pain.[8-10] It therefore follows that improving postoperative analgesia could greatly decrease the incidence of persistent postmastectomy pain.[11,12] Indeed, single-injection peripheral nerve blocks lasting less than 1 day have lowered persistent postmastectomy pain at 3 and 12 months.[13,14] Extending the peripheral nerve block 2 days with a continuous paravertebral nerve block further lowered the incidence of chronic pain.[15]

Cryoneurolysis is an analgesic technique consisting of the application of exceptionally low temperatures (approximately −70°C using nitrous oxide) to reversibly ablate peripheral nerves, resulting in prolonged pain relief termed "cryoanalgesia."[16] Originally, cryoneurolysis was administered *via* a surgical incision in which the target nerve was surgically exposed for direct treatment with a probe, greatly limiting applicability.[17] However, the development of probes that may be inserted percutaneously using ultrasound guidance enabled application without surgically exposing the target nerve(s).[18] The procedure is essentially the same as placing an ultrasound-guided peripheral nerve block; however, instead of injecting local anesthetic, a gas circulates through the probe inducing cold at the distal end and freezing the target nerve.[16] Nothing remains within the patient, and there is no external equipment to prepare, manage, or malfunction—a single administration results in effects measured in weeks to months without any subsequent patient or healthcare provider interventions.

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Although multiple case reports of perioperative ultrasound-guided percutaneous cryoneurolysis suggest substantial analgesic and opioid-sparing benefits after painful surgical procedures,[18] only a single randomized, controlled pilot study involving 12 patients having lower extremity procedures has been published.[19] We theorized that a single preoperative cryoneurolysis application would significantly lower postmastectomy acute and chronic pain, as well as associated opioid requirements. We therefore conducted a randomized, controlled study to evaluate the use of this modality for the treatment of pain after mastectomy to (1) determine the feasibility of and optimize the study protocol for a subsequent definitive clinical trial and (2) estimate analgesia and opioid reduction within the first postoperative year. The primary hypothesis tested was that the severity of surgically related pain would be lower on postoperative day 2 with the addition of cryoanalgesia compared with patients receiving solely standard-of-care treatment.

Materials and Methods

This study followed Good Clinical Practice and was conducted within the ethical guidelines outlined in the Declaration of Helsinki. The protocol was approved by the Institutional Review Board (University of California, San Diego, California) and prospectively registered (clinicaltrials.gov NCT03578237; Principal Investigator: Brian M. Ilfeld, M.D., M.S.; initial posting: July 6, 2018). Written, informed consent was obtained from all participants.

Participants

Enrollment was offered to adult patients at least 18 yr scheduled for uni- or bilateral mastectomy with a planned single-injection and continuous paravertebral nerve block for postoperative analgesia at a single enrolling center. Patients were excluded for (1) chronic analgesic use, including opioids (daily use within the 2 weeks before surgery and duration of use greater than 4 weeks); (2) pregnancy; (3) incarceration; (4) inability to communicate with the investigators; (5) morbid obesity (body mass index greater than 40 kg/m^2); and any contraindication specific to percutaneous cryoneurolysis, such as a localized infection at the treatment site, cold urticaria, cryofibrinogenemia, cryoglobulinemia, paroxysmal cold hemoglobinuria, and Raynaud's disease.

Immediately before surgery, participants had a single-injection paravertebral catheter inserted at T3 (surgery with anticipated axillary dissection) or T4 (no axillary dissection anticipated) in either a seated or prone position (patient preference) using a technique described previously.[6] Fifteen milliliters of ropivacaine, 0.5%, with epinephrine, 5 μg/ml, was injected through the perineural catheter with gentle aspiration every 3 ml. Catheter placement was considered successful if, within 30 min, the patient experienced any decreased sensation to cold temperature with an alcohol

pad over the approximate level of the ipsilateral third or fourth thoracic dermatome. Misplaced catheters were replaced successfully, or the patient was excluded from further study participation. For subjects undergoing bilateral mastectomy, with the use of the same protocol, a catheter was subsequently inserted on the contralateral side.

Treatment Group Assignment

After confirmation of successful perineural catheter insertion defined by sensory changes in the third or fourth intercostal nerve distribution, participants were randomly allocated to one of two treatments: (1) active cryoneurolysis or (2) sham. Computer-generated randomization lists were used by the University of California San Diego Investigational Drug Service (San Diego, California) to create sealed, opaque randomization envelopes enclosing the treatment group assignment. Randomization was stratified by laterality (unilateral *vs.* bilateral) in a 1:1 ratio in blocks of four (Statmate; GraphPad Software, San Diego, California). The investigator administering the study intervention opened the randomization envelope. Therefore, investigators, subjects, and clinical staff were masked to treatment group assignment, with the only exception being the unmasked individual who performed the procedure (and did not have subsequent contact with the participant).

Study Intervention

The second to fifth intercostal nerves were treated on the ipsilateral surgical side (in the final 20 participants, the first intercostal nerve was also treated for cases with axillary dissection). Using a curved-array transducer, the intercostal nerve was visualized using ultrasound just inferior to each treated rib immediately lateral to the costotransverse joint.

For the first 18 participants, a handheld cryoneurolysis machine was used (Iovera, Myoscience, Redwood City, California; before acquisition by Pacira Pharmaceuticals).[20] For subjects randomly assigned to sham, an intravenous cannula-type hollow-bore introducer was inserted just through the skin and a 90-mm probe (Iovera Smart Tip, Myoscience) subsequently inserted for the treatment duration to simulate a cryoneurolysis treatment. Because all subjects had a paravertebral block and the intercostal cryoneurolysis approach was *via* the participant's back and outside their line of vision, subjects remained masked to treatment group assignment. For subjects randomly assigned to receive cryoneurolysis, the same procedure was used, only with the introducer inserted deeper toward the target nerve, the probe situated adjacent to the intercostal nerve, and nitrous oxide passed through the probe resulting in cryoneurolysis. The specific number and duration of nitrous oxide cycles per treatment is proprietary for this device, but a light and tone indicate treatment conclusion.

For the remaining 42 participants, the handheld device was replaced by a cryoneurolysis console (PainBlocker, Epimed, Farmers Branch, Texas). Cryoneurolysis probes are available for the console that either (1) pass nitrous oxide to the tip inducing freezing temperatures or (2) vent the nitrous oxide at the base of the probe so that no gas reaches the probe tip, resulting in no temperature change. Importantly, these probes are indistinguishable in appearance and audible cues; therefore, investigators, participants, subjects, and all clinical staff were masked to treatment group assignment (with the exception of the treating physician performing the cryoneurolysis). The introducer was inserted beneath the ultrasound transducer and directed until immediately adjacent to the target nerve. The appropriate probe (active *vs.* sham) was inserted through the introducer and the cryoneurolysis device was triggered using 3 cycles of 2-min gas activation separated by 1-min defrost periods.[21]

Of note, it is impossible to mask the individual performing the cryoneurolysis procedure because the ice ball forming at the distal end of the probe—with active treatment—is clearly visible by ultrasound; and the lack of an ice ball for placebo subjects is equally clear (fig. 1).[22] It is essential to continuously visualize the probe and target nerve throughout the freeze/thaw cycles to ensure that (1) the entire nerve diameter is adequately treated and (2) the ice ball remains relatively motionless to prevent it from tearing surrounding tissue. This cannot be achieved if the ultrasound is turned off during nitrous oxide administration to mask the provider, and we prioritized patient safety over provider masking.

For all participants, the process was repeated for each treated intercostal nerve. For bilateral mastectomies, the entire process was repeated on the contralateral side with the same probe. Participants received a general anesthetic with intravenous propofol or inhaled volatile anesthetic in nitrous oxide and oxygen. Intravenous fentanyl was administered for cardiovascular responsiveness to noxious stimuli at the discretion of the anesthesia provider.

Postoperative Treatments

All participants received oral acetaminophen (975 mg four times daily) and a perineural infusion initiated before recovery room discharge: ropivacaine, 0.2%, at 8 ml/h, 4-ml bolus, and 30 (unilateral) or 60 (bilateral) min lockout. Administration of rescue analgesics for breakthrough pain was determined by pain severity using the numeric rating scale: oxycodone 5 mg (numeric rating scale less than 4) or 10 mg (numeric rating scale greater than or equal to 4). While the subject was hospitalized, pain was reassessed 30 min later and intravenous morphine (2 to 4 mg) was repeated every 30 min until the numeric rating scale was less than 4. Nonsteroidal anti-inflammatory drugs, gabapentin, ketamine, and other analgesics, were not permitted per

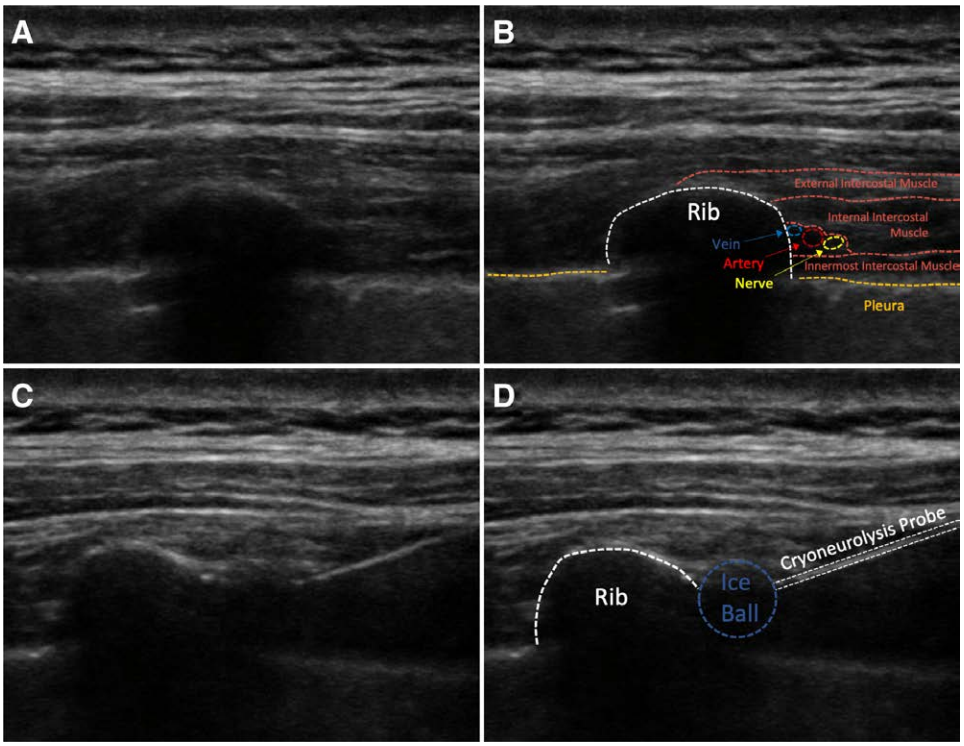

Fig. 1. Ultrasound images of percutaneous cryoneurolysis of an intercostal nerve.

the surgical service for the first postoperative month. Subjects remained hospitalized one to three nights and were subsequently discharged home after catheter removal by healthcare providers at approximately 6:00 AM the morning of discharge. Subjects and their caretakers were provided with contact information 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.

Unmasking

Observers were masked to treatment group assignment. After the full year of data collection for the first 30 participants, the treatment allocation of these individuals was unmasked exclusively for the principal investigator. Although not analyzed statistically, aggregated data were included as pilot data for a federal grant proposal (W81XWH-21-PRMRP-CTA). After study conclusion, the remainder of the group allocations were unmasked for the principal investigator who subsequently provided the dataset to the statistician for analysis in a masked fashion, with participants combined into unidentified "Treatment A" and "Treatment B" groups. After the completion of analysis, the study results were provided to each participant electronically and/or through the U.S. Postal Service.

Outcome Measurements (Endpoints)

We selected outcome measures that have established reliability and validity, with minimal inter-rater discordance, and are recommended for pain-related clinical trials by the World Health Organization and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement.[23] Outcomes were evaluated at baseline (before treatment) and on postoperative days 1, 2, 3, 4, 7, 14, and 21, as well as months 1, 3, 6, and 12. Baseline data and outcome measurements during hospitalization were collected in person, whereas all subsequent outcomes were collected by telephone. Staff blinded to treatment group assignment performed all measures and assessments.

Days 1 to 21

The numeric rating scale is a highly sensitive measure of pain intensity with numbers ranging from 0 to 10, zero equivalent to no pain and 10 equivalent to the worst imaginable pain; and is a valid and reliable measure for evaluating analgesic interventions.[24] Additionally, numeric rating scale scores correlate well with other measures of pain intensity,[25] and demonstrate high test–retest reliability.[26] These numeric rating scale characteristics led to World Health Organization and the Initiative on Methods, Measurement,

and Pain Assessment in Clinical Trials consensus recommendations for use of the 10-point numeric rating scale of pain intensity for pain trials.[23] Participants were asked to rate the "worst" (maximum) pain level they had experienced in the previous 24 h, as well as the "average" level of pain as measured using the numeric rating scale. The "average" pain score queried the afternoon of postoperative day 2 was designated as the primary outcome measure. If a patient responded with a range, the average of the range was recorded (*e.g.*, "two to three" was recorded as 2.5). Participants were also asked if they had difficulty sleeping due to pain (binary response: yes or no) and the number of awakenings due to pain the previous night. Last, participants were asked if they had experienced nausea rated on a 0 to 10 scale, with 10 equivalent to vomiting.

Months 1 to 12

The primary instrument was the Brief Pain Inventory (short form) that assesses pain and its interference with physical and emotional functioning.[27] The instrument includes three domains: (1) *pain* in the surgical site, with four questions using an numeric rating scale to evaluate four pain levels: "current," "least," "worst," and "average"; (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 seven interference questions involve general activity, mood, walking ability, normal work activities (both inside and outside the home), relationships, sleep, and enjoyment of life.[27] These seven functioning questions can be combined to produce an interference subscale (0 to 70). The use of both single items (*e.g.*, mood) and the composite scores is supported by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials consensus recommendations for assessing pain in clinical trials.[23,28] In addition, phantom pain—pain in a part of the body that no longer exists—and nonpainful phantom breast sensations during the previous 72 h were recorded for average intensity using the numeric rating scale, incidence, and average duration. Last, analgesic use for surgical area pain was recorded for both opioids and other medication classes.

Adverse events were recorded and reported to the Institutional Review Board. No compensation was provided to subjects for study participation.

Statistical Analysis

The sample size estimation was centered around the hypothesis that cryoneurolysis lowers the incidence and severity of postmastectomy pain in the week after surgery. To this end, the primary outcome measure was the average numeric rating scale (as administered as part of the Brief Pain Inventory) queried on the afternoon of postoperative day 2. The difference in the distribution of numeric rating scale between groups was assessed using the Mann-Whitney U test. The investigators approximated power using the two-sample *t* test. Assuming a SD of 2.25 points on the numeric rating scale, and a minimum clinically meaningful difference of two points on the numeric rating scale,[6] n = 30 patients per group provided 86% power with a two-sided $\alpha = 5\%$.

The *t* test approximation was confirmed by simulating integer-valued numeric rating scale scores in the range 0 to 10. One group was simulated by rounding normally distributed data with mean 1.5 and SD 2.5 (resulting in median of 2 and interquartile range 0 to 3); and the other with mean 3.5 and SD 2.5 (resulting in median of 4 and interquartile range 1 to 5).[6] When 10,000 trials were simulated under these assumptions, the Mann-Whitney U test provided 89.5% power, and Type I error was maintained at 4.85%.

Baseline characteristics of the randomized groups were summarized with means, standard deviations, and quartiles. Balance between groups was assessed following the approach described by Schober *et al.*[29] Specifically, standardized differences were calculated using Cohen's *d* whereby the difference in means or proportions was divided by the pooled SD estimates. Any key variables (*e.g.*, age, sex, height, weight, body mass index, etiology, laterality, and lymph node dissection) with an absolute standardized difference greater than $1.96\times\sqrt{2/n} = 0.506$, where n is the target sample size per group,[30] was noted and included in a sensitivity analysis with a generalized linear model (*e.g.*, logistic regression for incidence rates or linear regression for pain severity numeric rating scale) to obtain an estimate of the treatment effect adjusted for the imbalanced covariate(s). If key model assumptions were violated (*i.e.*, homoscedasticity or Gaussian distribution for linear models), data transformations and/or alternative generalized linear models were applied, as appropriate (Supplemental Digital Content, http://links.lww.com/ALN/C881). The primary analytic approach for this study included unadjusted two-sample Mann-Whitney U test or chi-square test for two proportions, as appropriate. No multiplicity adjustments were performed for this study. CIs associated with the Mann-Whitney U test are provided by normal approximations with continuity correction.[31] All tests were two-sided and $P < 0.05$ was considered statistically significant.

Secondary analyses included longitudinal linear model fit by generalized least-squares method controlling for any imbalanced covariates. Residuals were assumed to have an unstructured correlation and heterogeneous variance per time point. If estimation under those assumptions failed to converge, simpler assumptions were attempted, namely compound symmetric heterogeneous and finally compound symmetric with a power variance function of time.[32]

R version 3.4.4 (R-project.org) was used for sample size calculations and simulations. R version 4.1.1 (August 10, 2021) was used for analysis.

Results

Between August 2018 and March 2021, a total of 60 participants were enrolled, had successful paravertebral block administration and catheter insertion, and were randomly assigned to either active (n = 31) or sham (n = 29) cryoneurolysis (fig. 2). Among baseline characteristics (table 1), only the lymph node dissection rate was imbalanced between the two randomized groups with an absolute standardized difference of 0.557 (greater than an imbalance criterion of 0.506) and was adjusted for in sensitivity analyses. Age, height, weight, body mass index, laterality, and lymph node dissection exceeded the conventional absolute standardized difference threshold of 0.1 and were adjusted for in a second set of sensitivity analyses. One patient who had received cryoneurolysis withdrew from the study on postoperative

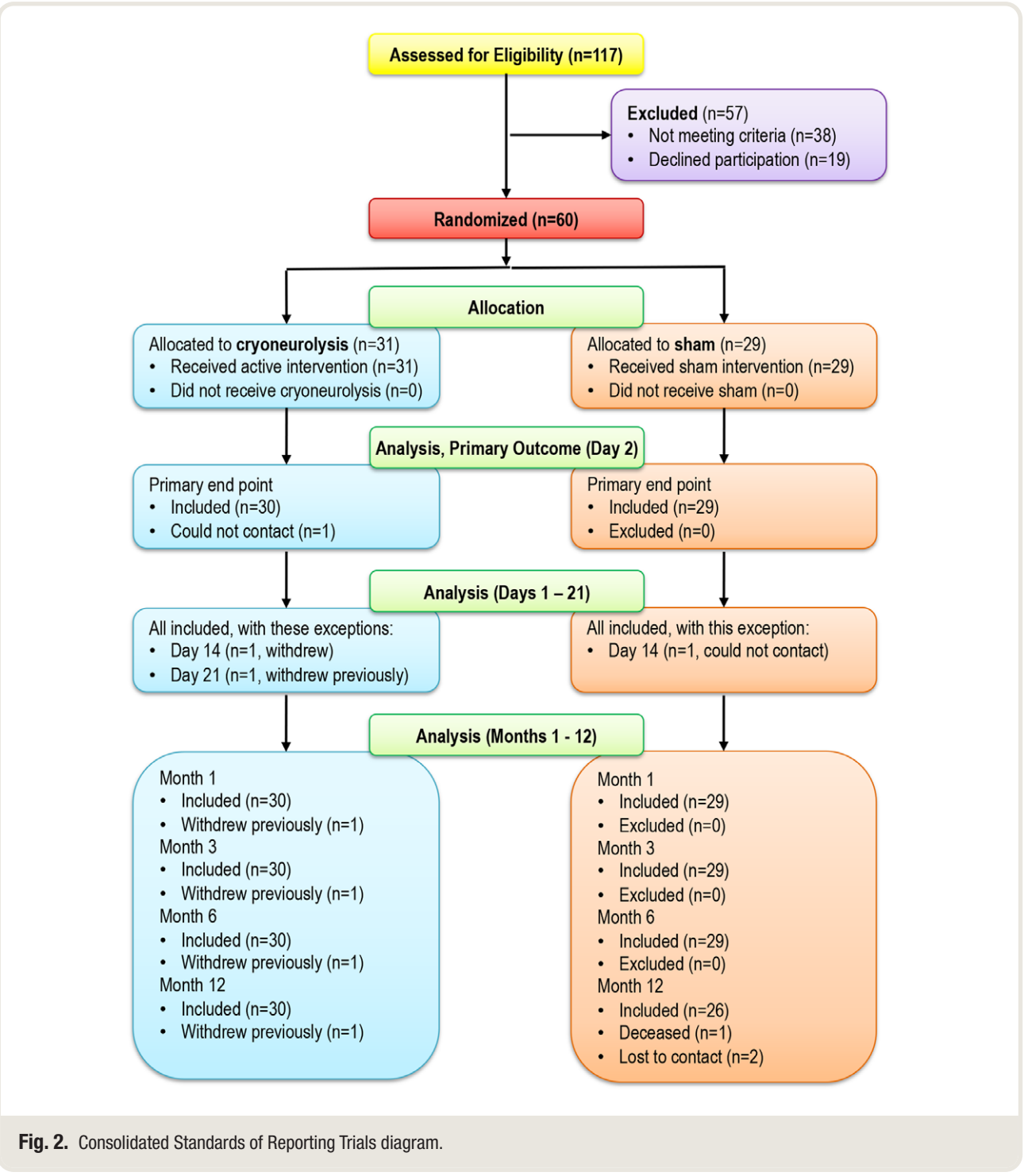

Fig. 2. Consolidated Standards of Reporting Trials diagram.

Table 1. Population, Procedural Information, and Day of Discharge.

	Cryoneurolysis (n = 31)	Sham (Placebo) (n = 29)	Absolute Standardized Difference
Age, yr	43 (35–54)	42 (36–59)	0.135
Female, %	100% (31)	100% (29)	—
Height, cm	163 (160–169)	163 (157–165)	0.235
Weight, kg	62 (55–67)	66 (55–76)	0.204
Body mass index, kg/m^2	23 (21–26)	25 (22–29)	0.345
Primary indication			0.030
Malignancy	84% (26)	83% (24)	
Prophylactic	16% (5)	17% (5)	
Laterality			0.426
Unilateral	35% (11)	48% (14)	
Bilateral	65% (20)	52% (15)	
Lymph node dissection	12 (39%)	19 (66%)	0.557
Day of discharge*			*P = 0.39*
1	3% (1)	3% (1)	
2	94% (29)	86% (25)	
3	3% (1)	10% (3)	

Values are reported as median (interquartile range) or percentage (number of subjects). Any variable with an absolute standardized difference greater than 0.506 was considered imbalanced.

* Totals not equal to 100% due to rounding error.

day 7 (she did not want to receive data collection phone calls). All patients were contacted and all outcomes were successfully collected with the exception of the one patient who withdrew (data missing for day 14 to month 12), one participant in the treated group at month 6, and 3 participants in the control group at month 12.

Primary Outcome

On postoperative day 2, participants who had received active cryoneurolysis had a median [interquartile range] pain score of 0 [0 to 1.4] *versus* 3.0 [2.0 to 5.0] in patients given sham: difference –2.5 (97.5% CI, –3.5 to –1.5), $P < 0.001$. Results were similar when adjusting for lymph dissection in a linear model (2.7 more points with sham, 95% CI, 1.8 to 3.6; $P < 0.001$) and a proportional odds model (odds of worst average pain on day 2 with the sham is 17.9, 95% CI, 5.6 to 57.1; $P < 0.001$).[33] The effect of lymph node dissection was not significant in either model. Results were also similar adjusting for all covariates with absolute standardized difference greater than 0.1 (2.5 more points with sham, 95% CI, 1.6 to 3.5; $P < 0.001$) or 18.7 odds of worse pain with sham (95% CI, 5.6 to 62.7; $P < 0.001$).

Secondary Outcomes

Worst (maximum) and average pain scores were lower for the active treatment group at each time point from days 1 to 21, as well as various other time points through month 6 (fig. 3). *Post hoc* analysis found that one participant in the cryoneurolysis group (3%) was discharged a day later than normal due to pain *versus* 3 (10%) in the control group ($P = 0.346$). Participants who had received active cryoneurolysis reported a complete absence of pain at a higher percentage than controls at each time point through month 12 (fig. 4). *Post hoc* analysis revealed that 48% of the treatment group experienced solely mild pain (numeric rating scale less than 4) throughout the entirety of the first year, compared with 10% of controls (fig. 5); and the highest pain score reported at any time point was a median (interquartile range) of 4.0 (2.8 to 5.3) for the treatment group, *versus* 7.0 (5.0 to 8.0) for controls (fig. 5). Thirteen percent of the cryoneurolysis group experienced no pain whatsoever during the year after surgery, *versus* none in the sham group ($P = 0.045$). No participant who had received cryoneurolysis reported phantom breast pain at any time point, compared with 10%, 17%, 13%, and 19% of the sham group reporting phantom pain (numeric rating scale more than 0) at months 1, 3, 6, and 12, respectively ($P = 0.11$, $P < 0.02$, $P < 0.04$, and $P = 0.01$, respectively). Results were similar in longitudinal models of pain outcomes adjusted for lymph node dissection.

Similarly, opioid consumption was lower for the active treatment group at each time point for days 1 to 14 (fig. 6). *Post hoc* analysis revealed that, during the first 3 weeks, cryoneurolysis lowered cumulative opioid use by 98%, with the treated group using 1.5 [0 to 14] mg of oxycodone compared with 75 [20 to 120] mg in controls ($P < 0.001$). Results were consistent in longitudinal models of opioid use adjusted for lymph node dissection. There was no opioid or other analgesic used for surgical pain by patients between 1 and 12 months. Fifty percent of the treatment group was opioid-free during the entire postoperative course (fig. 7), compared with only 14% of participants receiving sham ($P < 0.001$).

Pain's interference in physical and emotional functioning as measured with the Brief Pain Inventory (Interference

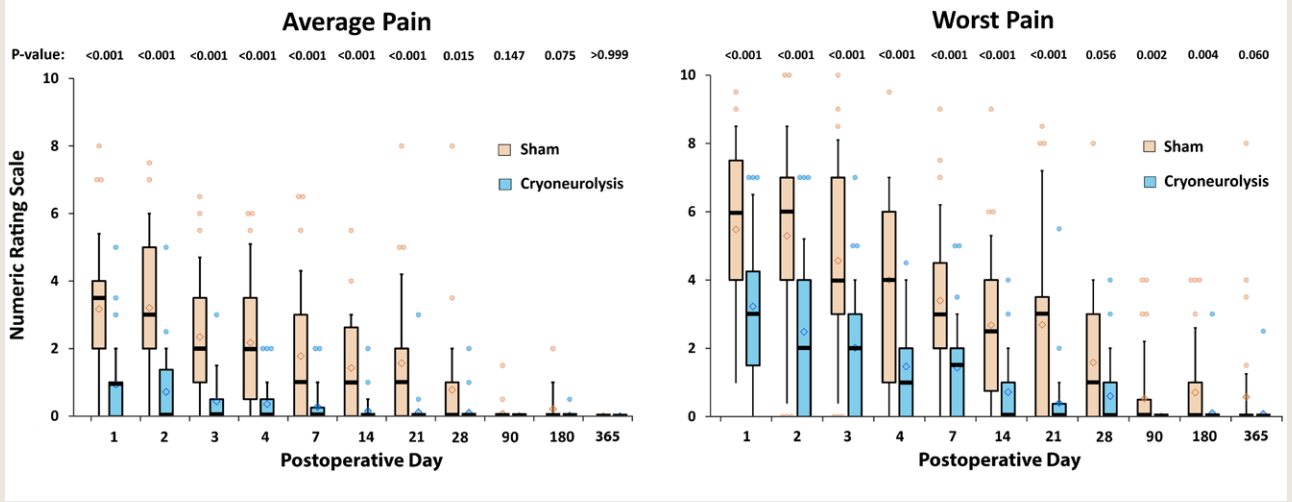

Fig. 3. Effects of percutaneous cryoneurolysis on *pain* in the first year after mastectomy. Includes pain severity at the surgical site (excludes phantom breast pain) and was measured using a numeric rating scale with 0 equivalent to no pain and 10 being the worst imaginable pain. Data expressed as median (*dark horizontal bars*) with 25th to 75th (*box*), 10th to 90th (*whiskers*), mean (*diamonds*), and outliers (*circles*).

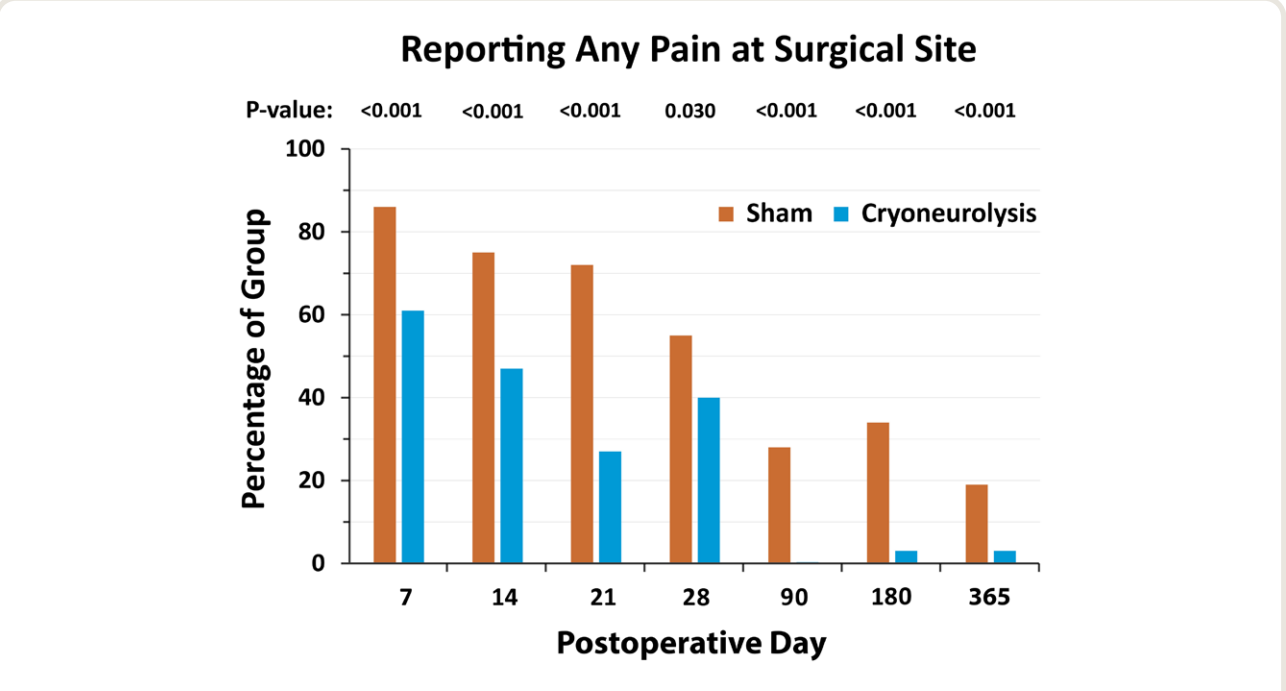

Fig. 4. Effects of percutaneous cryoneurolysis on the risk of experiencing *any* pain (numeric rating scale more than 0) at each time point in the year after mastectomy. *Post hoc* analysis results expressed as the percentage of each treatment group experiencing any pain (surgical or phantom) at each time point.

subscale) was very low in each group: median (interquartile range) for both groups of 0 (0 to 0) at all time points. Cryoneurolysis improved sleep quality and lessened the number of awakenings due to pain during the first 3 postoperative weeks (table 2).

Protocol Deviations and Adverse Events

The only protocol deviation was the study withdrawal on postoperative day 7 of one participant who had received cryoneurolysis due to an intolerance for the data collection phone calls. One participant experienced an anxiety

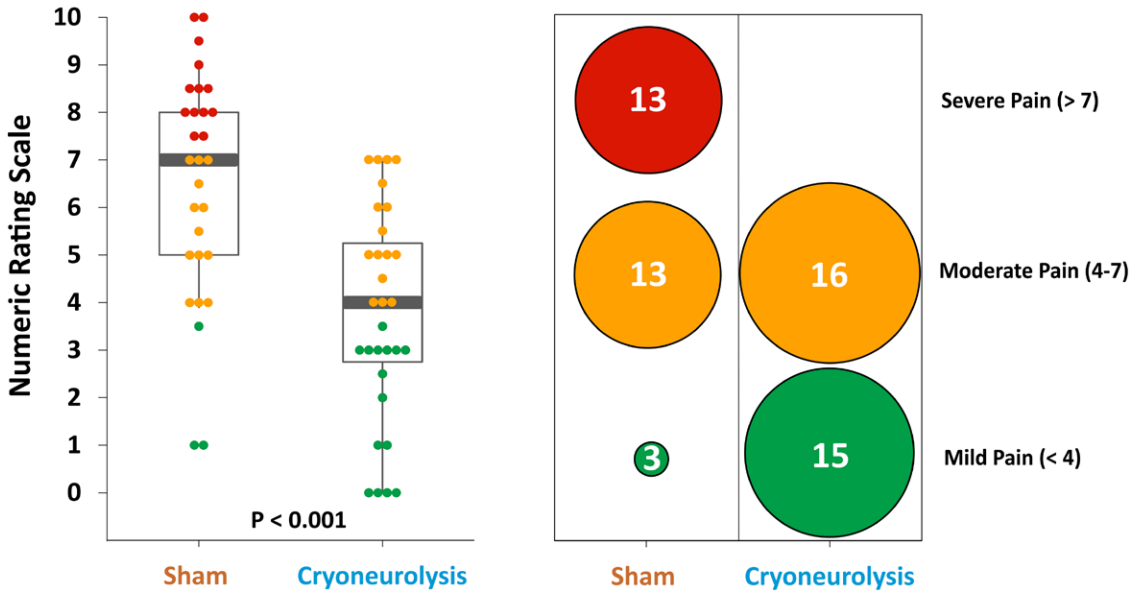

Fig. 5. Effects of percutaneous cryoneurolysis on the *maximum pain* level experienced in the *year* after mastectomy. Pain severity was measured using a numeric rating scale with 0 equivalent to no pain and 10 being the worst imaginable pain. *Post hoc* analysis results (*Left Panel*) expressed as median (*dark horizontal bars*) with 25th to 75th (*box*), 10th to 90th (*whiskers*), mean (*diamonds*), and outliers (*circles*); and (*Right Panel*) categorized as mild (numeric rating scale less than 4), moderate (numeric rating scale 4 to 7), and severe (numeric rating scale more than 7) pain.

attack when roused from her sedation after administration of her paravertebral nerve block and a sham study intervention. She subsequently underwent the surgical procedure and had an uneventful recovery. A different participant who had received a sham study procedure succumbed to metastasis-related complications and died between the 6th and 12th postoperative months. Neither adverse event was deemed related to study participation.

Discussion

This randomized, patient- and observer-masked, sham-controlled study provides evidence that a single preoperative application of ultrasound-guided percutaneous intercostal nerve cryoneurolysis markedly improved analgesia and reduced opioid requirements after mastectomy. Analgesic benefits continued beyond the expected duration of the cryoneurolysis treatment at the 3-, 6-, and 12-month time points, with chronic surgical pain reported in 1 (3%) treated patient compared with 5 (17%) controls after 1 yr. Through the entire first year, *post hoc* analysis revealed that 48% of the treatment group experienced exclusively mild pain (numeric rating scale less than 4), compared with only 10% of controls. No cryoneurolysis-related systemic side effects or complications were identified.

Depending on the application, various factors may favor percutaneous cryoneurolysis over opioid- or local anesthetic–based analgesics. First, and most obvious, cryoneurolysis has a duration of action measured in weeks and months after a single administration.[18] Cryoneurolysis avoids the systemic side effects related to opioid use such as nausea, sedation, and respiratory depression, and it has no potential for misuse, dependence, overdose, or diversion.[34] Unlike continuous peripheral nerve blocks, cryoneurolysis has no risk of local anesthetic–induced cardiac/neurologic toxicity, myotoxicity,[35] catheter dislodgement, local anesthetic leakage, or infusion pump malfunction.[36] Cryoneurolysis has a far lower patient and provider burden without a portable infusion pump, local anesthetic reservoir, and perineural catheter to carry, manage, and remove. In more than half a century of use, there has been only a single (suspected) cryoneurolysis-related infection reported,[37] *versus* a perineural catheter infection rate of up to 3%.[38]

A combination of attributes greatly limits cryoneurolysis application, including its prolonged—and unpredictable—duration of action, variable sensory, motor, and proprioceptive nerve block, and inability to withdraw or titrate effects.[18] However, when applied to intercostal nerves for mastectomy,[39] thoracotomy,[40] rib fracture,[41] or many other

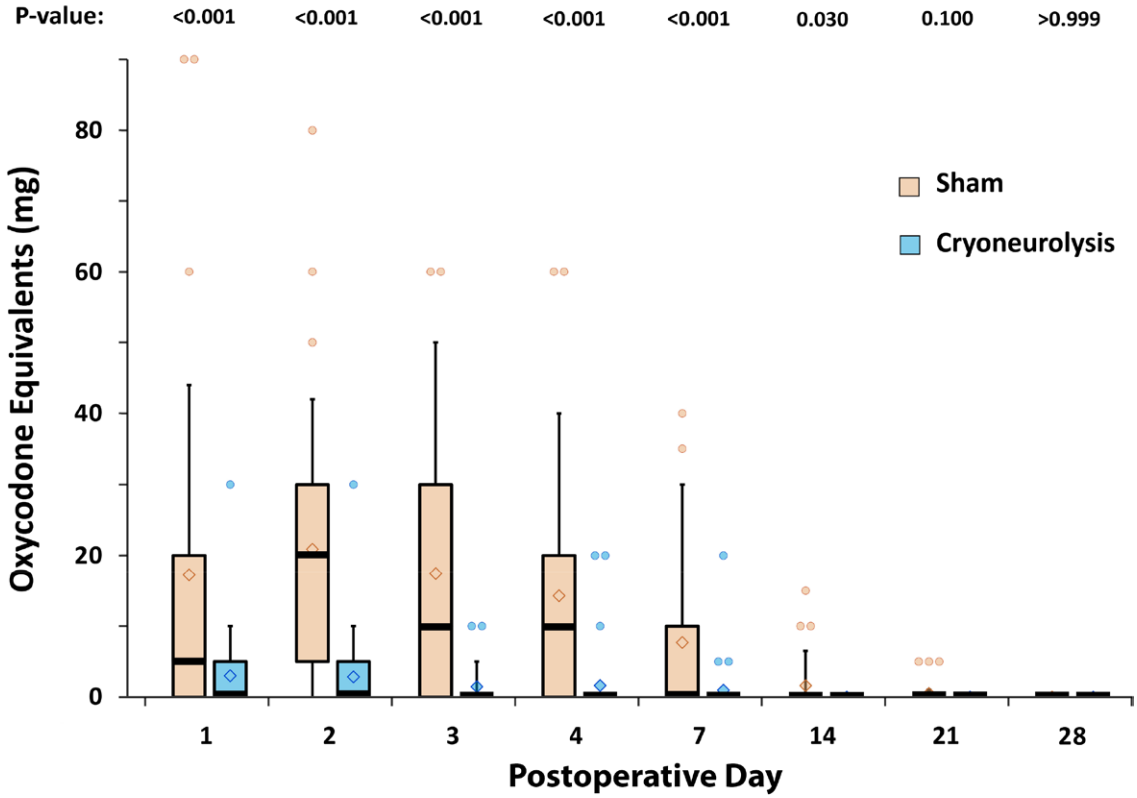

Fig. 6. Effects of percutaneous cryoneurolysis on *opioid consumption* in the immediate postoperative period after mastectomy. Data expressed in oxycodone equivalents as median (*dark horizontal bars*) with 25th to 75th (*box*), 10th to 90th (*whiskers*), mean (*diamonds*), and outliers (*circles*). During this period, cryoneurolysis lowered cumulative opioid use by 98%, with the treated group using 1.5 [0 to 14] mg of oxycodone compared with 75 [20 to 120] mg in controls ($P < 0.001$).

acute pain indications involving the thorax and abdomen, cryoneurolysis is a viable analgesic alternative. An additional limitation is the time for administration. For the current study, we used three 3-min cycles (2 min freeze, 1 min defrost) for four to five intercostal nerves, totaling approximately 40 to 50 min—doubled for bilateral mastectomies. Performing ultrasound-guided percutaneous cryoneurolysis before entering the operating room allows for parallel processing of patients and greatly decreases total operative time compared with intraoperative cryoneurolysis application; however, this duration is still a limitation of the technique. The optimal—or even minimal—freeze and defrost durations as well as the number of freeze-defrost cycles have yet to be determined.[18] Decreasing these values would reduce the time limitation of this modality, and future related research might increase the applicability of this modality.[42]

An additional possible limitation of cryoneurolysis has been suggested by two randomized, controlled trials reporting a greater frequency of transient neuropathic pain 3 to 6 months after open thoracotomy with *surgically* applied cryoneurolysis.[43,44] In contrast, the overwhelming majority of randomized, controlled trials involving surgical application have not reported similar findings.[40] Although a full discussion of this issue is outside the scope of this report, it has been hypothesized that physical manipulation of the target nerve before cryoneurolysis produces an afferent barrage that sets up central sensitization such that, when axonal regeneration occurs after injury, the fiber activity is perceived as dysesthetic.[18] If intraoperative nerve manipulation was the cause of a possibly higher incidence of transient neuropathic pain, then ultrasound-guided *percutaneous* cryoneurolysis should have no comparable risk. Indeed, to date, no occurrence of neuropathic pain has been associated with percutaneous administration,[45] and percutaneous cryoneurolysis has been successful in *treating* pre-existing neuropathic pain.[46] With more than five decades of clinical use and no published cases of permanent nerve injury,[47] this suggests a level of safety far surpassing traditional local anesthetic–based peripheral nerve blocks.[18,48,49]

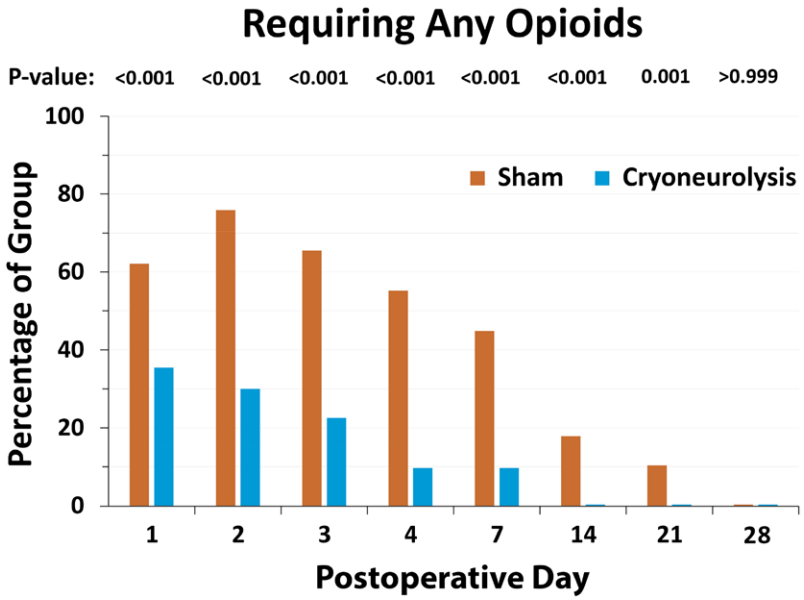

Fig. 7. Effects of percutaneous cryoneurolysis on the risk of requiring *any* opioids at each time point in the year after mastectomy. *Post hoc* analysis results expressed as the percentage of each treatment group consuming any opioids at each time point.

Table 2. Secondary Outcomes.

	Cryoneurolysis (n = 31)	Sham (Placebo) (n = 29)	*P* Value
Nausea and/or vomiting			
POD 1	3% (1)	10% (3)	0.269
POD 2	0% (0)	7% (2)	0.143
POD 3	0% (0)	3% (1)	0.297
POD 4	0% (0)	0% (0)	-
POD 7	0% (0)	3% (1)	0.297
POD 14	0% (0)	0% (0)	-
POD 21	0% (0)	0% (0)	-
Difficulty sleeping due to pain			
POD 1	7% (2)	31% (9)	0.014
POD 2	0% (0)	24% (7)	0.004
POD 3	7% (2)	28% (8)	0.028
POD 4	0% (0)	24% (7)	0.004
POD 7	3% (1)	24% (7)	0.017
POD 14	0% (0)	14% (4)	0.032
POD 21	0% (0)	21% (6)	0.009
Awakenings due to pain (# per subject)			
POD 1	0 (0, 0)	0 (0, 2.2)	0.004
POD 2	0 (0, 0)	0 (0, 1.0)	0.002
POD 3	0 (0, 0)	0 (0, 3.1)	0.021
POD 4	0 (0, 0)	0 (0, 1.2)	0.034
POD 7	0 (0, 0)	0 (0, 1.2)	0.025
POD 14	0 (0, 0)	0 (0, 1.0)	0.034
POD 21	0 (0, 0)	0 (0, 1.2)	0.009

Values are reported as percentage of the group (n), or median (10th percentile, 90th percentile)

POD, postoperative day

An important—and somewhat surprising—finding was that no participant who had received cryoneurolysis experienced phantom breast pain within the year after surgery. In contrast, participants within the control group experienced phantom pain at approximately the same incidence as reported in other investigations (10 to 19% between months 1 to 12).[50] In a previously published clinical trial performed at our own institution with the same principal surgeon, drawing from the same local population, and using a similar paravertebral block and postoperative infusion, participants reported exactly the same incidence of phantom breast pain at 3 months as in the control group of the current study (17%).[15] However, after 12 months, only 3% of the previous cohort reported phantom breast pain *versus* the 19% in the sham group of the current study.[15] Two differences between the two perineural infusion techniques was the longer duration (60 h) and high concentration of ropivacaine (0.4%) of the previous study compared with the less than 48-h duration and ropivacaine, 0.2%, of the current investigation.[6] The cryoneurolysis group of the current study had a similar incidence of phantom breast pain—0%—as the longer-duration, high-concentration ropivacaine perineural infusion of the previous study. This may be evidence that a longer, more-complete neural blockade reduces the risk of long-term phantom breast pain. Although requiring confirmation in a subsequent clinical trial, the findings of the current study provide additional evidence that preventive analgesia with a potent regional anesthetic provided for an adequate duration can lower the risk of developing

persistent postoperative pain, including both surgical and phantom breast pain.[7]

Our trial had features of a pilot study because it was undertaken to help plan a subsequent randomized trial by: (1) determining the feasibility of and optimizing the study protocol; and (2) estimating the treatment effect to adequately power the future investigation. However, the current project was powered for the prospectively defined primary outcome and the label "pilot" in no way lessens the veracity or validity of the results: what the findings are used for (*e.g.*, power estimation for an immediately subsequent larger trial) does not change the findings themselves. In fact, the treatment effect was much greater than what we had anticipated, concurrently reducing opioid consumption by 98% and pain throughout the entire 12-month study period. Consequently, the results were highly statistically significant for most endpoints, and our results thus stand on their own and indicate that percutaneous cryoneurolysis is highly effective treating pain after a mastectomy.

Limitations of this study limit the generalizability of our results and include (1) a limited sample size of 60 participants; (2) a single enrolling center; and (3) a secondary outcome measure that is unvalidated in which we used a nausea scale of 0 to 10 (0 equivalent to no nausea and 10 equivalent to vomiting). We did not stratify randomization for axillary dissection because the cryoneurolysis procedure was performed preoperatively, whereas the determination to perform an axillary dissection frequently occurs intraoperatively based on the results of an axillary lymph node biopsy. The lack of stratification resulted in an imbalance between groups, although we controlled for this imbalance statistically during the analysis.

In conclusion, percutaneous cryoneurolysis markedly improved analgesia and concurrently reduced opioid requirements free of systemic side effects and complications after uni- and bilateral mastectomy. Our results confirm the feasibility of a future larger trial and suggest protocol enhancements.

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Competing Interests

The institution of Drs. Ilfeld, Finneran, Swisher, Said, Gabriel, Sztain, and Khatibi has received funding from Epimed International (Farmers Branch, Texas) and Myoscience (Redwood City, California) for other research studies. The institution has also received funding and/or product for other research from SPR Therapeutics (Cleveland, Ohio), Infutronix (Natick, Massachusetts), and Avanos (Irvine, California). Dr. Trescot has served on an advisory board for Atricure (Mason, Ohio), and is the Chief Medical Officer for Stimwave Technologies (Pompano, Florida). Dr. Donohue has served on scientific advisory boards for Biogen (Cambridge, Massachusetts), Eli Lilly (Indianapolis, Indiana), and Neurotrack Technologies (Redwood City, California); and has consulted for Roche. His spouse is a full-time employee of Janssen (Beerse, Belgium). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: bilfeld@health.ucsd.edu. Raw data available at: bilfeld@health.ucsd.edu.

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References

1. Ghoncheh M, Pournamdar Z, Salehiniya H: Incidence and mortality and epidemiology of breast cancer in the world. Asian Pac J Cancer Prev 2016; 17:43–6
2. Kummerow KL, Du L, Penson DF, Shyr Y, Hooks MA: Nationwide trends in mastectomy for early-stage breast cancer. JAMA Surg 2015; 150:9–16
3. Steiner CA, Weiss AJ, Barrett ML, Fingar KR, Davis PH: Trends in Bilateral and Unilateral Mastectomies

in Hospital Inpatient and Ambulatory Settings, 2005-2013. Statistical Brief #201. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville, Maryland, 2006
4. Alaofi RK, Nassif MO, Al-Hajeili MR: Prophylactic mastectomy for the prevention of breast cancer: Review of the literature. Avicenna J Med 2018; 8:67–77
5. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA: Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol 2007; 25:5203–9
6. Ilfeld BM, Madison SJ, Suresh PJ, Sandhu NS, Kormylo NJ, Malhotra N, Loland VJ, Wallace MS, Proudfoot JA, Morgan AC, Wen CH, Wallace AM: Treatment of postmastectomy pain with ambulatory continuous paravertebral nerve blocks: A randomized, triple-masked, placebo-controlled study. Reg Anesth Pain Med 2014; 39:89–96
7. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367:1618–25
8. Habib AS, Kertai MD, Cooter M, Greenup RA, Hwang S: Risk factors for severe acute pain and persistent pain after surgery for breast cancer: a prospective observational study. Reg Anesth Pain Med 2019; 44:192–9
9. Meretoja TJ, Leidenius MHK, Tasmuth T, Sipila R, Kalso E: Pain at 12 months after surgery for breast cancer. JAMA 2014; 311:90–2
10. Wang L, Guyatt GH, Kennedy SA, Romerosa B, Kwon HY, Kaushal A, Chang Y, Craigie S, de Almeida CPB, Couban RJ, Parascandalo SR, Izhar Z, Reid S, Khan JS, McGillion M, Busse JW: Predictors of persistent pain after breast cancer surgery: A systematic review and meta-analysis of observational studies. CMAJ 2016; 188:E352–61
11. Meijuan Y, Zhiyou P, Yuwen T, Ying F, Xinzhong C: A retrospective study of postmastectomy pain syndrome: Incidence, characteristics, risk factors, and influence on quality of life. ScientificWorldJournal 2013; 2013:159732
12. Peuckmann V, Ekholm O, Rasmussen NK, Groenvold M, Christiansen P, Moller S, Eriksen J, Sjogren P: Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. Eur J Pain 2009; 13:478–85
13. Qian B, Huang S, Liao X, Wu J, Lin Q, Lin Y: Serratus anterior plane block reduces the prevalence of chronic postsurgical pain after modified radical mastectomy: A randomized controlled trial. J Clin Anesth 2021; 74:110410
14. Fujii T, Shibata Y, Akane A, Aoki W, Sekiguchi A, Takahashi K, Matsui S, Nishiwaki K: A randomised controlled trial of pectoral nerve-2 (PECS 2) block vs. serratus plane block for chronic pain after mastectomy. Anaesthesia 2019; 74:1558–62
15. Ilfeld BM, Madison SJ, Suresh PJ, Sandhu NS, Kormylo NJ, Malhotra N, Loland VJ, Wallace MS, Mascha EJ, Xu Z, Wen CH, Morgan AC, Wallace AM: Persistent postmastectomy pain and pain-related physical and emotional functioning with and without a continuous paravertebral nerve block: A prospective 1-year follow-up assessment of a randomized, triple-masked, placebo-controlled study. Ann Surg Oncol 2015; 22:2017–25
16. Trescot AM: Cryoanalgesia in interventional pain management. Pain Physician 2003; 6:345–60
17. Gage AA: History of cryosurgery. Semin Surg Oncol 1998; 14:99–109
18. Ilfeld BM, Finneran JJ: Cryoneurolysis and percutaneous peripheral nerve stimulation to treat acute pain. Anesthesiology 2020; 133: 1127–49
19. Finneran IV JJ, Schaar AN, Swisher MW, Godat LN, Lee JG, Higginson SM, Ilfeld BM: Percutaneous cryoneurolysis of the lateral femoral cutaneous nerve for analgesia following skin grafting: A randomized, controlled pilot study. Reg Anesth Pain Med 2022; 47:60–1
20. Ilfeld BM, Preciado J, Trescot AM: Novel cryoneurolysis device for the treatment of sensory and motor peripheral nerves. Expert Rev Med Devices 2016; 13:713–25
21. Gill W, Fraser J, Carter DC: Repeated freeze-thaw cycles in cryosurgery. Nature 1968; 219:410–3
22. Kastler A, Gruber H, Gizewski E, Loizides A: Ultrasound assessment of ice-ball formation by cryoneurolysis device in an ex vivo model. Reg Anesth Pain Med 2018; 43:631–3
23. Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, Chappell A, Chartier K, Cleeland CS, Costello A, Cowan P, Dimitrova R, Ellenberg S, Farrar JT, French JA, Gilron I, Hertz S, Jadad AR, Jay GW, Kalliomaki J, Katz NP, Kerns RD, Manning DC, McDermott MP, McGrath PJ, Narayana A, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Reeve BB, Rhodes T, Sampaio C, Simpson DM, Stauffer JW, Stucki G, Tobias J, White RE, Witter J: Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain 2010; 149:177–93
24. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L: Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998; 280:1837–42
25. Gilron I, Jensen MP: Clinical trial methodology of pain treatment studies: selection and measurement of self-report primary outcomes for efficacy. Reg Anesth Pain Med 2011; 36:374–81
26. Lundeberg T, Lund I, Dahlin L, Borg E, Gustafsson C, Sandin L, Rosen A, Kowalski J, Eriksson SV: Reliability and responsiveness of three different pain assessments. J Rehabil Med 2001; 33:279–83

27. Cleeland CS, Ryan KM: Pain assessment: Global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994; 23:129–38
28. Turk DC, Dworkin RH, Burke LB, Gershon R, Rothman M, Scott J, Allen RR, Atkinson JH, Chandler J, Cleeland C, Cowan P, Dimitrova R, Dionne R, Farrar JT, Haythornthwaite JA, Hertz S, Jadad AR, Jensen MP, Kellstein D, Kerns RD, Manning DC, Martin S, Max MB, McDermott MP, McGrath P, Moulin DE, Nurmikko T, Quessy S, Raja S, Rappaport BA, Rauschkolb C, Robinson JP, Royal MA, Simon L, Stauffer JW, Stucki G, Tollett J, von Stein T, Wallace MS, Wernicke J, White RE, Williams AC, Witter J, Wyrwich KW: Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. Pain 2006; 125:208–15
29. Schober P, Vetter TR: Correct baseline comparisons in a randomized trial. Anesth Analg 2019; 129:639
30. Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009; 28:3083–107
31. Hollander M, Wolfe DA: Nonparametric Statistical Methods. New York, John Wiley & Sons, 1973
32. Pinheiro JC, Bates DM: Mixed-Effects Models in S and S-Plus, Springer, 2000
33. Manuguerra M, Heller GZ, Ma J: Continuous ordinal regression for analysis of visual analogue scales: The R package ordinalCont. J Stat Software 2020; 96:1–25
34. Kharasch ED, Brunt LM: Perioperative opioids and public health. Anesthesiology 2016; 124:960–5
35. Neal JM, Salinas FV, Choi DS: Local anesthetic-induced myotoxicity after continuous adductor canal block. Reg Anesth Pain Med 2016; 41:723–7
36. Ilfeld BM: Continuous peripheral nerve blocks: An update of the published evidence and comparison with novel, alternative analgesic modalities. Anesth Analg 2017; 124:308–35
37. Cahani D, Chacko J, Hahn B: Myonecrosis: A rare complication of cryoneurolysis. J Emerg Med 2019; 57:e73–6
38. Capdevila X, Bringuier S, Borgeat A: Infectious risk of continuous peripheral nerve blocks. Anesthesiology 2009; 110:182–8
39. Gabriel RA, Finneran JJ, Swisher MW, Said ET, Sztain JF, Khatibi B, Wallace AM, Hosseini A, Trescot AM, Ilfeld BM: Ultrasound-guided percutaneous intercostal cryoanalgesia for multiple weeks of analgesia following mastectomy: a case series. Korean J Anesthesiol 2020; 73:163–8
40. Khanbhai M, Yap KH, Mohamed S, Dunning J: Is cryoanalgesia effective for post-thoracotomy pain? Interact Cardiovasc Thorac Surg 2014; 18:202–9
41. Finneran JJ, Gabriel RA, Swisher MW, Berndtson AE, Godat LN, Costantini TW, Ilfeld BM: Ultrasound-guided percutaneous intercostal nerve cryoneurolysis for analgesia following traumatic rib fracture–A case series. Korean J Anesthesiol 2020; 73:455–9
42. Garibyan L, Moradi Tuchayi S, Wang Y, Khodorova A, Stemmer-Rachamimov A, Purschke M, Osseiran S, Evans CL, Mao J, Strichartz G, Anderson RR: Neural selective cryoneurolysis with ice slurry injection in a rat model. Anesthesiology 2020; 133: 185–94
43. Ju H, Feng Y, Yang BX, Wang J: Comparison of epidural analgesia and intercostal nerve cryoanalgesia for post-thoracotomy pain control. Eur J Pain 2008; 12:378–84
44. Mustola ST, Lempinen J, Saimanen E, Vilkko P: Efficacy of thoracic epidural analgesia with or without intercostal nerve cryoanalgesia for postthoracotomy pain. Ann Thorac Surg 2011; 91:869–73
45. Bittman RW, Peters GL, Newsome JM, Friedberg EB, Mitchell JW, Knight JM, Prologo JD: Percutaneous image-guided cryoneurolysis. AJR Am J Roentgenol 2018; 210:454–465
46. Yoon JH, Grechushkin V, Chaudhry A, Bhattacharji P, Durkin B, Moore W: Cryoneurolysis in patients with refractory chronic peripheral neuropathic pain. J Vasc Interv Radiol 2016; 27:239–43
47. Zhou L, Craig J, Parekh N: Current concepts of neurolysis and clinical applications. J Analgesics 2014; 2:16–22
48. Neal JM, Barrington MJ, Brull R, Hadzic A, Hebl JR, Horlocker TT, Huntoon MA, Kopp SL, Rathmell JP, Watson JC: The second ASRA practice advisory on neurologic complications associated with regional anesthesia and pain medicine: Executive summary 2015. Reg Anesth Pain Med 2015; 40:401–30
49. Ilfeld BM: Continuous peripheral nerve blocks: a review of the published evidence. Anesth Analg 2011; 113:904–25
50. Dijkstra PU, Rietman JS, Geertzen JH: Phantom breast sensations and phantom breast pain: a 2-year prospective study and a methodological analysis of literature. Eur J Pain 2007; 11:99–108