Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Thursday, 23 November, 2023
1800 HOURS

LOCATION:
Thai House Cuisine Kingston
185 Sydenham Street #183, Kingston, ON
K7K 3M1

PRESENTING ARTICLES:
Dr. Ian Gilron & Dr. Toros Canturk

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

ANESTHESIOLOGY

Preoperative Paravertebral Block and Chronic Pain after Breast Cancer Surgery: A Double-blind Randomized Trial

Aline Albi-Feldzer, M.D., Sylvain Dureau, Pharm.D., Abdelmalek Ghimouz, M.D., Julien Raft, M.D., Jean-Luc Soubirou, M.D., Guillaume Gayraud, M.D., Christian Jayr, M.D.

Anesthesiology 2021; 135:1091–103

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Chronic pain after breast surgery is common, both causing suffering and limiting function.
- Previous studies suggest that paravertebral blocks may prevent chronic pain after breast surgery, but the data are limited.

What This Article Tells Us That Is New

- More than 350 study participants undergoing mastectomy were randomized to either paravertebral blocks with ropivacaine or saline injections. Both groups received multimodal analgesia.
- Although paravertebral block using ropivacaine had a small analgesic effect in the immediate postoperative period, no differences in pain 3, 6, and 12 months after surgery were detected.

ABSTRACT

Background: The effectiveness of paravertebral block in preventing chronic pain after breast surgery remains controversial. The primary hypothesis of this study was that paravertebral block reduces the incidence of chronic pain 3 months after breast cancer surgery.

Methods: In this prospective, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, 380 women undergoing partial or complete mastectomy with or without lymph node dissection were randomized to receive preoperative paravertebral block with either 0.35 ml/kg 0.75% ropivacaine (paravertebral group) or saline (control group). Systemic multimodal analgesia was administered in both groups. The primary endpoint was the incidence of chronic pain with a visual analogue scale (VAS) score greater than or equal to 3 out of 10, 3 months after surgery. The secondary outcomes were acute pain, analgesic consumption, nausea and vomiting, chronic pain at 6 and 12 months, neuropathic pain, pain interference, anxiety, and depression.

Results: Overall, 178 patients received ropivacaine, and 174 received saline. At 3 months, chronic pain was reported in 93 of 178 (52.2%) and 83 of 174 (47.7%) patients in the paravertebral and control groups, respectively (odds ratio, 1.20 [95% CI, 0.79 to 1.82], $P = 0.394$). At 6 and 12 months, chronic pain occurred in 104 of 178 (58.4%) *versus* 79 of 174 (45.4%) and 105 of 178 (59.0%) *versus* 93 of 174 (53.4%) patients in the paravertebral and control groups, respectively. Greater acute postoperative pain was observed in the control group 0 to 2 h (area under the receiver operating characteristics curve at rest, 4.3 ± 2.8 *vs.* 2.9 ± 2.8 VAS score units × hours, $P < 0.001$) and when maximal in this interval (3.8 ± 2.1 *vs.* 2.5 ± 2.5, $P < 0.001$) but not during any other interval. Postoperative morphine use was 73% less in the paravertebral group (odds ratio, 0.272 [95% CI, 0.171 to 0.429]; $P < 0.001$).

Conclusions: Paravertebral block did not reduce the incidence of chronic pain after breast surgery. Paravertebral block did result in less immediate postoperative pain, but there were no other significant differences in postoperative outcomes.

(ANESTHESIOLOGY 2021; 135:1091–103)

Chronic pain after breast cancer surgery is frequent and an important healthcare priority because of its effect on quality of life. Although the association between the severity of acute pain after surgery and the likelihood of chronic pain is known, their causal relationship has not been clarified. We previously showed that wound infiltration with ropivacaine did not reduce the incidence or severity of pain after breast surgery.[1] Thus, other authors have used paravertebral block rather than infiltration to improve pain control after breast surgery. One recent, single-center, double-blind study including 172 patients with similar outcomes to our study showed that ultrasound-guided multilevel paravertebral block lowered the incidence of chronic pain 3 months (35% *vs.* 51% of patients) and 6 months (22% *vs.* 37%) after partial mastectomy with or without axillary lymph node dissection. Another recent study including 2,132 patients from 13 hospitals evaluated the recurrence of breast cancer after regional or general anesthesia, with the incidence of chronic pain as a secondary outcome.[2] Incisional pain was identical in the two groups at 6 months (52% in each group) and 1 yr (27% *vs.* 28%). A Cochrane review on chronic pain also found that paravertebral block reduced chronic pain after breast surgery

This article is featured in "This Month in Anesthesiology," page A1. This article has a visual abstract available in the online version.

Submitted for publication November 26, 2020. Accepted for publication August 10, 2021. Published online first on October 7, 2021. From the Department of Anesthesiology, Institut Curie, PSL Research University, Saint-Cloud, France (A.A.-F., C.J.); the Biometry Unit (S.D.) and the Department of Anesthesiology (A.G.), Institut Curie, Paris Sciences & Lettres University, Paris, France; the Department of Anesthesiology, Centre Alexis Vautrin, Nancy, France (J.R.); the Department of Anesthesiology, Centre Leon Berard, Lyon, France (J.-L.S.); and the Department of Anesthesiology, Centre Jean Perrin, Clermont–Ferrand, France (G.G.).

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but graded the evidence as low.[3] Another recent review and meta-analysis[4] concluded that the data on chronic pain for paravertebral block are too scarce to be conclusive. The quality of evidence was considered to be low, mainly due to a lack of adequate blinding. Nonetheless, although the existing evidence is weak and conflicting, there is increasing interest in the role of paravertebral block in preventing chronic pain after breast cancer surgery.[3,4]

Therefore, this prospective, multicenter, randomized, double-blind, parallel-group, placebo-controlled study in a large homogenous population evaluated the effect of paravertebral block with ropivacaine on acute and chronic pain as well as on comorbidities, such as anxiety and depression, after complete or partial mastectomy with or without axillary or sentinel lymph node dissection for cancer.

The primary hypothesis of this study was that preoperative ultrasound-guided paravertebral block reduces the incidence of chronic pain. The primary endpoint was the incidence of chronic pain greater than or equal to 3 out of 10 on a 0 to 10 visual analogue scale (VAS) 3 months after breast surgery. The secondary outcomes were acute postoperative pain at rest or during mobilization, the extent of sensory blockade, complications of paravertebral block, the consumption of analgesics, and nausea and vomiting every 30 min for 2 h in the postanesthesia care unit (PACU) and every 6 h for 48 h after surgery. Chronic pain was also evaluated 6 months and 1 yr after surgery.

Materials and Methods

Study Design and Number of Participants

This large, prospective, randomized (1:1), multicenter (four cancer centers), double-blind, parallel-group, placebo-controlled trial was approved by the institutional review board (Institut Curie, Saint-Cloud, France) of the study ethics review committee (Hospital Ambroise Paré, Boulogne, France) and was registered in ClinicalTrials.gov (NCT02408393), Aline Albi-Feldzer, April 2015. The trial was conducted in accordance with the original protocol with minor changes. Following the recommendations of the French Society of Anesthesiologists (Paris, France), preoperative blood tests were performed if necessary, depending on clinical status rather than systematically in each patient.

The number of patients in the study was determined using the Casagrande and Pike formula.[5] Based on previous results,[1] the expected effect size was calculated to detect a 50% incidence reduction in chronic pain (30% to 15% of patients) 3 months after surgery. With a bilateral α risk of 5% and 90% power, 179 patients were needed per group, for a total of 358. To account for loss to follow-up or consent withdrawals, the number of patients was increased to 391.

Inclusion and Randomization

Three hundred ninety-one women aged 18 to 85 yr with an American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status of I, II, or III who were admitted for mastectomy with or without axillary lymph node or sentinel lymph node dissection or partial mastectomy (sparing the skin, areola, and nipple) with axillary lymph node dissection were included in the study. The study was explained by an anesthesiologist during the preoperative consultation.

The exclusion criteria included male sex; a life expectancy less than 2 yr; active malignant disease; pregnant or breastfeeding women; bilateral surgery; ipsilateral breast surgery in the past 3 yr; preoperative chronic pain; allergy to local anesthetics, steroids, or morphine; a reported history of substance abuse; local skin inflammation at the puncture area; and an inability to comply with the protocol for any reason.

All patients gave written informed consent, and enrollment ceased when the target sample size was reached.

The research assistant checked for eligibility and informed consent and then enrolled the participants. The statistician generated the allocation sequence on a computer. The patients were randomly allocated (1:1) into two groups using a Web site random number generator with Tenalea software (Netherlands Cancer Institute, The Netherlands). Randomization was stratified by center and the type of surgery: partial mastectomy with axillary lymph node dissection, and mastectomy with or without axillary lymph node dissection or sentinel lymph node dissection.

The results of the randomization were given to the pharmacist, who prepared a syringe with ropivacaine or normal saline solution (0.35 ml/kg) within 24 h before surgery. The syringe was sealed in a sterile envelope and sent to the PACU. The nurse opened the sequentially numbered envelope containing the syringe with the solution.

The paravertebral group received 0.35 ml/kg ropivacaine 0.75% in the paravertebral space without exceeding a total volume of 30 ml. The control group also received an equal volume of saline (0.35 ml/kg) in the paravertebral space. All attending anesthesiologists, patients, nurses, and data collectors were blinded to the group assignment.

Procedure

No premedication was given before surgery.

In the preoperative holding area located in the PACU, standard monitoring included electrocardiography, pulse oximetry, capnography, and noninvasive blood pressure monitoring. Oxygen (2 $l \cdot min^{-1}$) was delivered through nasal prongs.

The patients were placed in the lateral position on the opposite side from surgery, and remifentanil administration was started with an IV targeted effect-site concentration objective to reach a concentration of 2 $ng \cdot ml^{-1}$.

The second thoracic paravertebral space (T2) was scanned by ultrasonography (Model Alpinion E-cube i7 [Alpinion Medical Systems, Korea]) with a 2- to 5-MHz ultrasound probe (linear array L3-8H). The probe was positioned on the transverse plane against the spinal

process. Under aseptic conditions, a 22-gauge 80-mm needle (SonoTAP [Pajunk, Germany]) was advanced in an "in-plane" direction toward the paravertebral space, immediately above the pleura and below the costotransverse ligament. The position of the needle was confirmed by the descent of the pleura when injecting 2 to 3 ml of saline solution for hydrolocalization.

Then, 0.35 ml · kg^{-1} ropivacaine 0.75% was injected with intermittent negative aspiration tests every 5 ml, without exceeding a total of 30 ml or an equivalent volume of saline.

Immediately after the paravertebral block injection procedure was completed in the preoperative holding area, the intensity of pain from the procedure was evaluated with a VAS, the remifentanil injection was discontinued, and the patients were transferred to the operating room 30 min later. Then, 20 min after the procedure, the dermatome block level to temperature was measured by another anesthesiologist to map the spread of blocked dermatomes. An ice cube was placed in the finger of a disposable plastic glove and used to perform the cold sensation test. Patients were given a reference cold sensation at the third cervical dermatome before each measurement. The blocked area was tested between the midaxillary and midclavicular lines from the fourth thoracic dermatome in the cranial and caudal directions, and the sensation in each dermatome on the blocked side was compared to the reference sensation. Persistence of any cold sensation was considered to be an absence of sensory block. The peak sensory cephalad block and caudal block levels were assessed, and then the number of blocked dermatomes was recorded.

The patient was positioned on the operating table and fitted with monitors, including a Bispectral Index. Then, general anesthesia was induced with an IV bolus of propofol (2.5 mg · kg^{-1}) that was administered when the IV remifentanil targeted effect-site concentration reached 4 ng · ml^{-1}. If necessary, cisatracurium besilate (0.1 mg/kg) or atracurium (0.05 mg/kg) was injected to facilitate insertion of the tracheal tube, or a second-generation laryngeal mask (Ambu, Denmark) was secured in the pharynx. Volume-controlled mechanical ventilation was initiated using 6 ml · kg^{-1} of predicted body weight tidal volume, 5 cm H_2O of positive end expiratory pressure, and a 40% inspired oxygen concentration.

Anesthesia was maintained with inhaled sevorane (1 to 2% end-expiratory concentration) or desflurane (3 to 4% end-expiratory concentration) combined with nitrous oxide (50%) and IV remifentanil using a targeted effect-site concentration ranging from 2 to 4 ng · ml^{-1}. The inhaled sevorane or desflurane concentrations and remifentanil effect-site targets were continuously adapted to the monitor (40 < Bispectral Index < 60, and hemodynamics, respectively) outputs. The patient was extubated at the end of surgery after reversal of the neuromuscular block, if necessary.

Antiemetic prophylaxis and postoperative pain prevention were systematically provided with an IV injection of 8 mg dexamethasone on induction, and paracetamol (1,000 mg), ketoprofen (100 mg), and omeprazole (40 mg) 60 min before surgery was expected to be completed. The laryngeal mask or tracheal tube was removed in the operating room, and the patients were transferred to the PACU.

The postoperative intensity of pain at rest and during ipsilateral anterior arm and shoulder elevation was measured upon arrival in the PACU, every 30 min for the first 2 postoperative hours, then every 6 h of the hospital stay, using a VAS ranging from 0 (no pain at all) to 10 (worst imaginable pain). In the presence of a VAS score greater than 3/10 at rest in the PACU, rescue IV morphine was titrated using 2-mg boluses administered every 5 min (no upper limit of dosage). The patients remained in the PACU until the VAS score was less than or equal to 3.

The surgical patients systematically received oral ketoprofen (100 mg) every 12 h. If more analgesia was needed, the first-line treatment was oral paracetamol (1,000 mg) every 6 h when the VAS score was greater than 3, and the second-line treatment was oral tramadol (100 mg) twice a day. In the case of postoperative nausea and vomiting, ondansetron (4 mg) and droperidol (1.25 mg) were given every 8 h IV on demand.

Outcomes

The primary objective of this study was to evaluate the effect of ultrasound-guided single-injection paravertebral block with ropivacaine on the incidence of chronic pain at the surgical site 3 months after major breast surgery. Chronic pain was defined as pain at the surgical site greater than or equal to 3 out of 10 on item 5 of the Brief Pain Inventory (item 5: "Please rate your pain by circling the one number that best describes your pain on the average in the past 24 h, no pain = 0, worst pain = 10"). The Brief Pain Inventory[6] is a multidimensional pain assessment tool that measures pain severity and interference (0 to 10). Pain severity was measured by four items: worst pain, least pain, average pain in the last 24 h, and pain now. The seven interference items (sleep disturbances, general activity, mood, work, relations with others, walking, and enjoyment of life) were assessed on a 0 to 10 scale, with 0 being "did not interfere" and 10 being "interfered completely."

The following early secondary endpoints were evaluated: distribution of a diminished cold sensation (ice cube test) 15 min and 24 h after the paravertebral injection, acute pain assessed with a VAS (no pain = 0, worst pain = 10) at rest and mobilization every 30 min for 2 h in the PACU and every 6 h for 48 h, satisfaction with the quality of acute pain management, any episodes of paravertebral block–related complications, postoperative nausea and vomiting, total morphine and analgesic consumption for 48 h, and immediate complications or side effects.

Late secondary endpoints were also evaluated: chronic pain according to item 5 of the Brief Pain Inventory and other parameters of the Brief Pain Inventory at 6 months and 12 months; pain characterized with the Douleur Neuropathique 4 score at 3, 6, and 12 months and the Hospital Anxiety Depression Scale questionnaire; and any episodes of late complications, side effects, or paravertebral block–related complications.

Three subscale scores that can be generated with the Brief Pain Inventory were added to the analysis[7,8]: the average score of all seven items of the Brief Pain Inventory (Brief Pain Inventory—Pain Interference Total Score), physical interference (the average score of work, general activity, and walking from the Brief Pain Inventory), and affective interference (the average score of relations with others, enjoyment of life, and mood from the Brief Pain Inventory). The sleep item was excluded from the physical interference scale because the multidimensional scaling analysis revealed that the pain interference items clustered into two groups and that the sleep item was separated from those two clusters. Thus, according to the Brief Pain Inventory manual, the average score of work, general activity, and walking from the Brief Pain Inventory subscale is recommended.

Questionnaires at 3, 6, and 12 months were sent by mail, and patients were contacted by telephone 3, 6, and 12 months after surgery if they did not return the questionnaires.

Statistical Analysis

The intent-to-treat population was defined as all randomized patients, but 28 patients withdrew their consent before surgery. Therefore, these patients were excluded from the intent-to-treat population. Some patients did not receive the entire assigned treatment (fig. 1) but remained in the intent-to-treat population and were excluded from the per-protocol population, which only included patients who received a paravertebral injection. The demographic and clinical characteristics of the patients are described. Nominal (type of surgery, treatments, complications) and ordinal (American Society of Anesthesiologists Physical Status) data are presented as numbers and percentages, excluding missing data. Ratio-scaled quantitative data (age and postoperative treatment doses) are presented as mean ± SD. The interval scaled data (VAS score during injection) and the ratio scaled data of remifentanil doses are presented as median with interquartile range. Comparisons between the two groups were only performed for the dose of remifentanil and pain during injection in the paravertebral space. In these two cases, due to nonhomogeneous variances, data were presented as median with interquartile range instead of mean ± SD. The Mann–Whitney U test was used because we compared only two groups, the control and the paravertebral group.

The incidence of pain 3 months after surgery greater than or equal to 3 on the VAS for item 5 of the Brief Pain Inventory (primary endpoint) was expressed as a percentage with the 95% CI according to the treatment group in the intent-to-treat population. A Pearson chi-square test was performed to compare the results of the Brief Pain Inventory at 3 months, and the odds ratio was estimated using logistic regression and presented with the 95% CI. Missing values for the primary endpoint in the intent-to-treat population were considered to be failures, *i.e.*, the presence of chronic pain at 3 months. Sensitivity analyses were performed on the per-protocol population. Missing values were successively considered, as in the intent-to-treat population, as failures, completed by multiple imputations of the analysis or excluded. Data imputation was computed from the table 1 variables using multiple imputation by chained equations. Five imputations resulted in five complete datasets. Then the results obtained for each dataset were pooled in a global imputation result. All analyses for the primary endpoint were performed without stratification for the randomization strata (site and type of surgery).

Post hoc exploratory subgroup analyses of the primary endpoint were performed. The subgroup results according to the treatment arm were assessed by logistic regression models and presented in the form of a forest plot with odds ratios and interaction *P* values. The secondary outcomes were analyzed in the per-protocol population. Postoperative pain over time (VAS score) was plotted for each patient, and the area under the receiver operating characteristics curve (AUC) was then estimated for each patient. The mean AUCs were compared according to the randomization arm using two independent samples *t* tests. The difference in perioperative opioid requirements was assessed with a logistic regression model with 0 for patients who did not receive morphine and 1 for those who received morphine. Blocked dermatomes and answers to the Brief Pain Inventory, Hospital Anxiety Depression Scale, and Douleur Neuropathique 4 questionnaires are represented using bar plots and histograms. Comparisons between the two groups for blocked dermatomes at 15 min and 24 h were performed with Pearson chi-square tests.

All tests were two-tailed, and $P < 0.05$ was considered to be significant. All analyses were performed using R software (version 4.0.2; R Core Team, Austria).

Results

We screened 391 patients for participation in this study from March 27, 2015, to June 3, 2018. Eleven of these patients did not meet the inclusion criteria, resulting in 380 randomized patients. Twenty-eight of these patients withdrew their consent after randomization and before surgery. Randomization was performed the day before surgery. Eighteen patients changed their minds after randomization and before surgery mainly due to fear of the paravertebral block and ineffectiveness of the saline injection. The type of surgery changed in 10 patients, and they withdrew their consent. Therefore, the final population in the intent-to-treat population analysis included 352 patients. Fifteen of

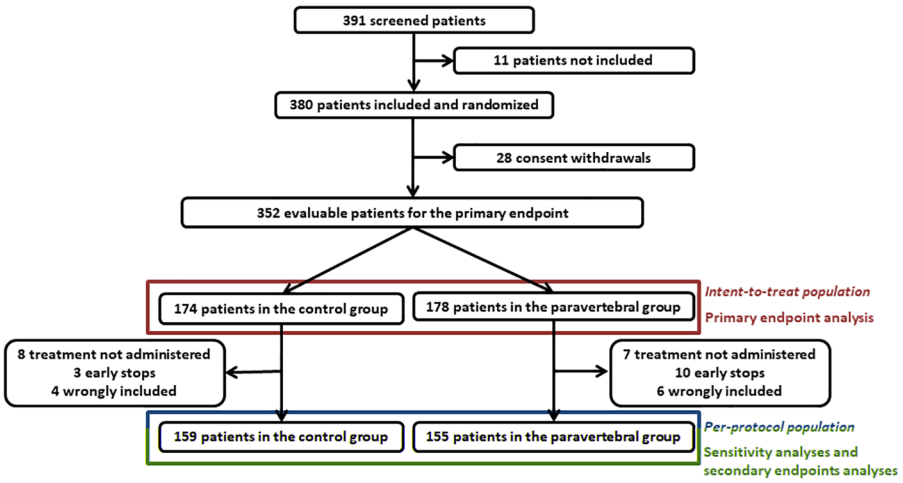

Fig. 1. Flowchart. Control group: thoracic paravertebral block with saline.

these patients were excluded from the paravertebral group and 23 from the placebo group due to a breach in protocol. Thus, the 314 remaining patients received treatment, completed the study, and constituted the per-protocol population (fig. 1). The population characteristics, treatments, and complications in each arm are described in table 1. The characteristics were similar between the two arms, particularly in average age (58 yr).

The primary endpoint of this trial was the incidence of chronic pain greater than or equal to 3 on a 0 to 10 scale for item 5 of the Brief Pain Inventory 3 months after breast surgery. Patients were considered to have pain if the pain score was greater than or equal to 3 and to be pain-free if the score was less than 3 for the fifth item of the Brief Pain Inventory. In the intent-to-treat population, there were 93 of 178 (52.2%) and 83 of 174 (47.7%) patients in the paravertebral block and control groups with pain greater than or equal to 3 on the Brief Pain Inventory 3 months after surgery, respectively. The associated odds ratio, with the control group as a reference, was 1.20 (95% CI, 0.79 to 1.82; $P = 0.394$). In this analysis, any missing data for the fifth item of the Brief Pain Inventory at 3 months (43 of 174 patients in the control group and 46 of 178 in the paravertebral group) was considered to be a failure, and thus was considered to be pain (table 2). Sensitivity analyses were then performed in the per-protocol population; the missing values of Brief Pain Inventory (32 of 159 patients in the control and 33 of 155 in the paravertebral group) were successively considered as failures, completed by multiple imputations of the analysis, or excluded, as described above. The same results were obtained as in the intent-to-treat analysis (table 2).

In all situations, the results obtained were similar and led to the same conclusion: there was no difference between the control group and paravertebral group in pain at 3 months according to the Brief Pain Inventory. There was also no difference for secondary outcomes at 6 and 12 months. Chronic pain was reported in 104 of 178 (58.4%) patients in the paravertebral group and 79 of 174 (45.4%) in the control group at 6 months and in 105 of 178 (59.0%) and 93 of 174 (53.4%) at 12 months (fig. 2). Subgroup analyses were performed to detect any subgroups with a beneficial effect. The results are shown in a forest plot (fig. 3). Paravertebral block with ropivacaine tended to have a beneficial effect on pain at 3 months in patients who underwent partial mastectomy but was associated with more pain in patients who underwent mastectomy, although the difference is not statistically significant.

Evaluations of the blocked dermatomes were performed with the ice test at 15 min and 24 h. At 15 min, there were significantly more patients with at least one blocked dermatome in the paravertebral group than in the control group (84.8% [95% CI, 77.7 to 90.3] *vs.* 43.7% [95% CI, 35.4 to 52.2]; $P < 0.001$). Although still observed between the two arms at 24 h, the difference was less marked (78.2% [95% CI, 69.9 to 85.1] *vs.* 64.9% [95% CI, 56.1 to 73.0]; $P = 0.019$) (fig. 4). Ninety-two percent of the patients in the paravertebral group experienced loss of cold sensation either 15 min or 24 h after the injection, which persisted in 78% of patients after 24 h, with a reduction in the lower dermatome blockade from the sixth thoracic intercostal nerve to the fifth (fig. 4).

Acute postoperative pain was measured every 30 min in the PACU for the first 2 h and then every 6 h for 48 h. The VAS scores were plotted for each patient at each time point, and the profile of pain scores was determined for each patient. From surgery to 48 h after surgery, the profile of pain scores was very similar between the two groups at rest and during mobilization. AUCs were determined for each

Table 1. Demographic and Clinical Characteristics of the Intent-to-treat Population

	Control Group (n = 174)		Paravertebral Group (n = 178)	
Quantitative data	n (missing values)	mean ± SD or median (interquartile range)	n (missing values)	mean ± SD or median (interquartile range)
Nominal and ordinal data	n (%)		n (%)	
Demographics				
Age, yr, mean ± SD	174 (0)	58 ± 13	178 (0)	58 ± 14
Body mass index, kg/m²				
< 25	94 (54.3)		85 (47.8)	
≥ 25	79 (45.7)		93 (52.3)	
Missing values	1		0	
ASA Physical Status				
1	27 (15.6)		32 (18.0)	
2	137 (79.2)		140 (78.7)	
3	9 (5.2)		6 (3.4)	
Missing values	1		0	
Surgical information				
Type of surgery				
Mastectomy	6 (3.5)		11 (6.2)	
Mastectomy + axillary lymph node dissection	73 (42.2)		70 (39.3)	
Mastectomy + sentinel lymph node dissection	68 (39.3)		74 (41.6)	
Partial mastectomy + axillary lymph node dissection	25 (14.5)		23 (12.9)	
Partial mastectomy + sentinel lymph node dissection	1 (0.6)		0 (0)	
Missing values	1		0	
Intraoperative variables				
Remifentanil during surgery (maintenance dose)				
No	4 (2.4)		3 (1.8)	
Yes	161 (97.6)		163 (98.2)	
Missing values	9		12	
Total dose of remifentanil, µg,* median (interquartile range)	150 (24)	344 (245–434)	135 (43)	276 (210–384)
Pain during injection, VAS score,† median (interquartile range)	150 (24)	6 (3–7)	145 (33)	2 (0–4)
Postoperative treatments				
Intravenous morphine titration				
No	49 (30.1)		101 (61.2)	
Yes	114 (69.9)		64 (38.8)	
Missing values	11		13	
Dose of morphine, mg, mean ± SD	111 (3)	6 ± 3	63 (1)	6 ± 3
Tramadol during the 48 h after surgery				
No	139 (79.9)		142 (79.8)	
Yes	35 (20.1)		36 (20.2)	
Total dose of tramadol during the 48 h after surgery, mg, mean ± SD	35 (0)	150 ± 100	36 (0)	150 ± 100
Paracetamol during the 48 h after surgery				
No	64 (36.8)		79 (44.4)	
Yes	110 (63.2)		99 (55.6)	
Total dose of paracetamol during the 48 h after surgery, g, mean ± SD	110 (0)	3 ± 2	99	3 ± 2
Ketoprofen during the 48 h after surgery				
No	32 (18.4)		39 (21.9)	
Yes	142 (81.6)		139 (78.1)	
Total dose of ketoprofen during the 48 h after surgery, mg, mean ± SD	142 (32)	300 ± 150	139 (39)	300 ± 100
Postoperative complications				
Immediate complications				
No	155 (93.4)		160 (94.1)	
Claude Bernard Horner syndrome	1 (0.6)		9 (5.3)	
Pain during injection with feeling of pressure in the thorax and chest	10 (6.0)		0 (0)	
Motor blockade in the arm of the operated side	0 (0)		1 (0.6)	
Missing values	8		8	
Complications during the first 48 h				
No	161 (95.8)		162 (96.4)	
Hematoma of the surgical site	4 (2.4)		2 (1.2)	
Hematoma of the surgical site with necessity of surgery	2 (1.2)		1 (0.6)	
Pain at the paravertebral block puncture site	0 (0)		1 (0.6)	
Pain at the surgical drain	1 (0.6)		2 (1.2)	
Missing values	6		10	
Nausea and/or vomiting immediately after the injection				
No	157 (90.2)		166 (93.3)	
Yes	17 (9.8)		12 (6.7)	
Nausea and/or vomiting in the first 48 h				
No	161 (92.5)		167 (93.8)	
Yes	13 (7.5)		11 (6.2)	

Nominal (type of surgery, treatments, complications) and ordinal (ASA Physical Status) data are presented as numbers and percentages, excluding missing data. Ratio-scaled quantitative data (age and postoperative treatment doses) are presented as mean ± SD. The interval scaled data (VAS score during injection) and the ratio-scaled data of remifentanil doses are presented as median with interquartile range. Comparisons between the two groups were only performed for the dose of remifentanil and pain during injection in the paravertebral space. In these two cases, due to nonhomogeneous variances, data were presented as median with interquartile range instead of mean ± SD. The Mann–Whitney U test was performed because we compared only two groups, the control group and the paravertebral group.

*Mann–Whitney U test: $P < 0.01$. †Mann–Whitney U test: $P < 0.001$.

ASA, American Society of Anesthesiologists; VAS, visual analogue scale.

Table 2. Results of the Primary Outcome Analysis and Sensitivity Analyses

Population	Class	Control Group, n (%)	Paravertebral Group, n (%)	Odds Ratio (95% CI)	*P* Value
Intent-to-treat		174	178		
Missing data considered as failures for item 5 of Brief Pain Inventory: VAS score < or ≥ 3	Score < 3	91/174 (52.3%)	85/178 (47.8%)	1.20 (0.79–1.82)	*P* = 0.394
	Score ≥ 3	83/174 (47.7%)	93/178 (52.2%)		
Per-protocol		159	155		
Missing data considered as failures for item 5 of Brief Pain Inventory: VAS score < or ≥ 3	Score < 3	89/159 (56.0%)	80/155 (51.6%)	1.19 (0.76–1.86)	*P* = 0.438
	Score ≥ 3	70/159 (44.0%)	75/155 (48.4%)		
Per-protocol		159	155		
Missing data were treated by multiple imputations, item 5 of Brief Pain Inventory: VAS score < or ≥ 3	Score < 3	110/159 (69.2%)	101/155 (65.2%)	1.18 (0.98–1.42)	*P* = 0.142
	Score ≥ 3	49/159 (30.8%)	54/155 (34.8%)		
Per-protocol		127	122		
Missing data for Brief Pain Inventory were excluded, item 5 of Brief Pain Inventory: VAS score < or ≥ 3	Score < 3	89/127 (70.1%)	80/122 (65.6%)	1.23 (0.72–2.10)	*P* = 0.447
	Score ≥ 3	38/127 (29.9%)	42/122 (34.4%)		

The main analysis, as specified in the protocol, is supposed to for the intent-to-treat population and consider all patients even if there are missing data. For the primary outcome analysis, missing values for the fifth item of the Brief Pain Inventory (43 of 174 patients in the control group and 46 of 178 in the paravertebral group) were considered as failures, *i.e.*, pain equal to or higher than 3 for the fifth item of the Brief Pain Inventory. Sensitivity analyses were performed on the per-protocol population with missing values (32 of 159 patients in the control group and 33 of 155 in the paravertebral group). In the first case, missing values were considered, as in the intent-to-treat population, as failures. In the second case, missing values were completed by multiple imputations of the analysis. In the third case, the missing values were excluded. In all situations, the results obtained were similar and led to the same conclusion: there was no difference between the control group and paravertebral group in pain at 3 months according to the Brief Pain Inventory.

VAS, visual analogue scale.

patient and compared. The mean AUCs at rest were 34.9 ± 32.2 and 31.7 ± 34.1 VAS score units × hours in the control and paravertebral groups, respectively. There was no significant difference in the mean AUCs between the two groups ($P = 0.388$). The mean AUC during mobilization was 50.4 ± 47.6 VAS score units × hours in the control group and 44.9 ± 44.8 VAS score units × hours in the paravertebral group ($P = 0.288$). However, a comparison of the 2-h postoperative period showed greater acute postoperative pain in the control group at rest (AUC, 4.3 ± 2.8 *vs.* 2.9 ± 2.8 VAS score units × hours, $P < 0.001$; maximum pain score, 3.8 ± 2.1 *vs.* 2.5 ± 2.5 VAS score units, $P < 0.001$) and during mobilization (AUC, 3.7 ± 3.2 *vs.* 2.5 ± 2.5 VAS score units × hours, $P < 0.001$; maximum pain score, 4.0 ± 2.2 *vs.* 2.4 ± 2.5 VAS score units, $P < 0.001$; fig. 5). Fewer patients required morphine in the paravertebral group, 64/165 (38.8%) *versus* 114/163 (69.9%) in the control group (odds ratio, 0.272 [95% CI, 0.171 to 0.429]; $P < 0.001$).

When patients required morphine, the doses were similar in the two groups: 6 ± 3 mg and 6 ± 3 mg in the control and paravertebral groups, respectively (table 1).

There was no difference in the incidence of nausea and vomiting, analgesic consumption over 48 h, or patient satisfaction between the two groups (table 1).

At 3, 6, and 12 months, the Hospital Anxiety Depression Scale and Douleur Neuropathique 4 scores were similar in the two groups (fig. 2 and appendix).

Nine patients presented with Claude Bernard Horner syndrome in the paravertebral group, while 10 and 6 patients in the control and paravertebral groups reported that the injection was painful with a feeling of pressure in the thorax and chest, respectively (table 1).

Discussion

This multicenter, prospective, randomized, double-blind, placebo-controlled study shows that paravertebral block with ropivacaine and systemic multimodal analgesia did not reduce the incidence of chronic pain 3 months after breast surgery (primary endpoint of the study) compared to paravertebral block with saline and systemic multimodal analgesia. These results are similar to some other studies[2,9,10] that did not demonstrate a long-term benefit with paravertebral block analgesia despite a short-term benefit[3,4] but do not agree with the results of other studies.[11,12] Two recent meta-analyses showed no statistically significant reduction in the risk of persistent postoperative pain 3 to 12 months after breast cancer surgery.[3,13] These 2 studies included seven and six trials, respectively, with an overlap of 3 studies; thus, 2 out of 10 studies found paravertebral block to be beneficial.[11,14] In one of the recent abovementioned meta-analyses,[3] the number of treated patients needed for an additional beneficial outcome was 7 (95% CI, 6 to 13), and the evidence was considered low-quality. There were also conflicting results in two other recent studies.[2,12] One

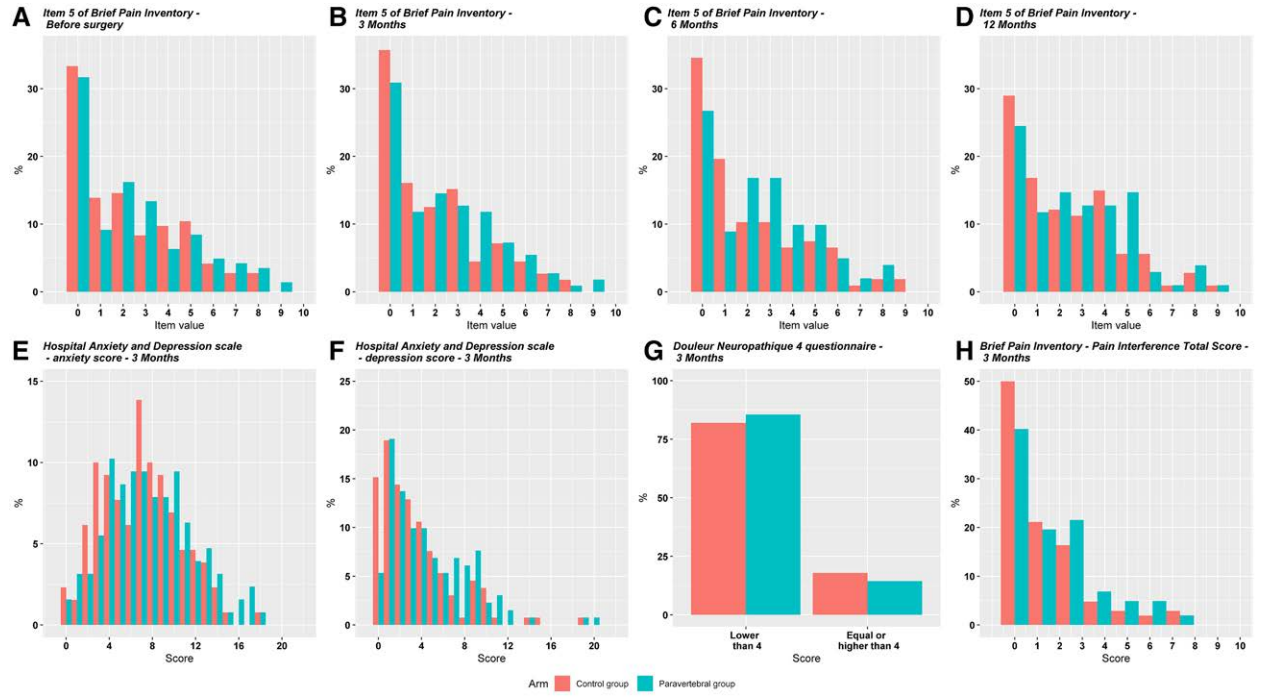

Fig. 2. Brief Pain Inventory before surgery and 3, 6, and 12 months after surgery and Hospital Anxiety and Depression Scale and Douleur Neuropathique 4 questionnaire scores 3 months after surgery. Pain interference at 3 months after surgery was assessed with the Brief Pain Inventory (sleep disturbances, general activity, mood, work, relations with others, walking, and enjoyment of life). The Brief Pain Inventory measures pain severity and interference. Pain severity is measured by four items: worst pain, least pain, average pain in the last 24 h, and pain now. The seven interference items (sleep disturbance, general activity, mood, work, relations with others, walking, and enjoyment of life) are assessed on a 0 to 10 scale, with 0 being "did not interfere" and 10 being "interfered completely." Three subscale scores can be generated: Pain Interference Total Score (the average score of all seven items), physical interference (the average score of work, general activity, and walking), and affective interference (the average score of relations with others, enjoyment of life, and mood). The complete figure with all items is in the appendix. (*A–D*) Brief Pain Inventory, item 5: before surgery and 3, 6, and 12 months after surgery. (*E*) Hospital Anxiety and Depression Scale: anxiety score 3 months after surgery. (*F*) Hospital Anxiety and Depression Scale: depression score 3 months after surgery. (*G*) Douleur Neuropathique 4 questionnaire score equal to or higher than 4 evaluated 3 months after surgery. (*H*) Brief Pain Inventory—Pain Interference Total Score: seven interference items (sleep disturbances, general activity, mood, work, relations with others, walking, and enjoyment of life) 3 months after surgery.

study that reported a lower incidence of chronic pain at 3 and 6 months in the paravertebral group was limited by the absence of pain evaluation during mobilization, and of sensory blockade tests. Moreover, mastectomies were only partial.[12] The second study found that the incidence and severity of persistent postoperative incisional breast pain at 6 and 12 months were unaffected by the analgesia technique. However, pain was not the primary outcome, and the study had several limitations: no reduction in postoperative morphine consumption in the paravertebral group, no sensory blockade tests, and no placebo group for the paravertebral block; thus, the study was not double-blind.[2] The overall incidence of chronic pain at 3 months in our study (53% and 48% in the paravertebral block and control groups, respectively) was similar to that in other published studies (30 to 65%). The wide range of prevalence of chronic pain reported in the literature is probably due to several factors such as the definition and the pain score. Different pain scores might provide different results. A moderate or greater pain score (greater than or equal to 3) is clinically relevant after breast surgery. Less than 3 would be considered mild.

Our study also showed the absence of a statistically significant reduction in the incidence of chronic and neuropathic pain at 3, 6, and 12 months, despite better control of acute pain, which could have been due to the short-term benefit of postoperative pain relief in the paravertebral group. Although we also used numerous tools to identify pain-related functional interference, including the Brief Pain Inventory; Hospital Anxiety Depression Scale; Pain Interference Total Score from the Brief Pain Inventory; the average score of work, general activity, and walking from Brief Pain Inventory; and average score of relations with others, enjoyment of life, and mood from Brief Pain Inventory, no differences in these items were found between the two groups. These scores on patient outcome provide more precise information than pain

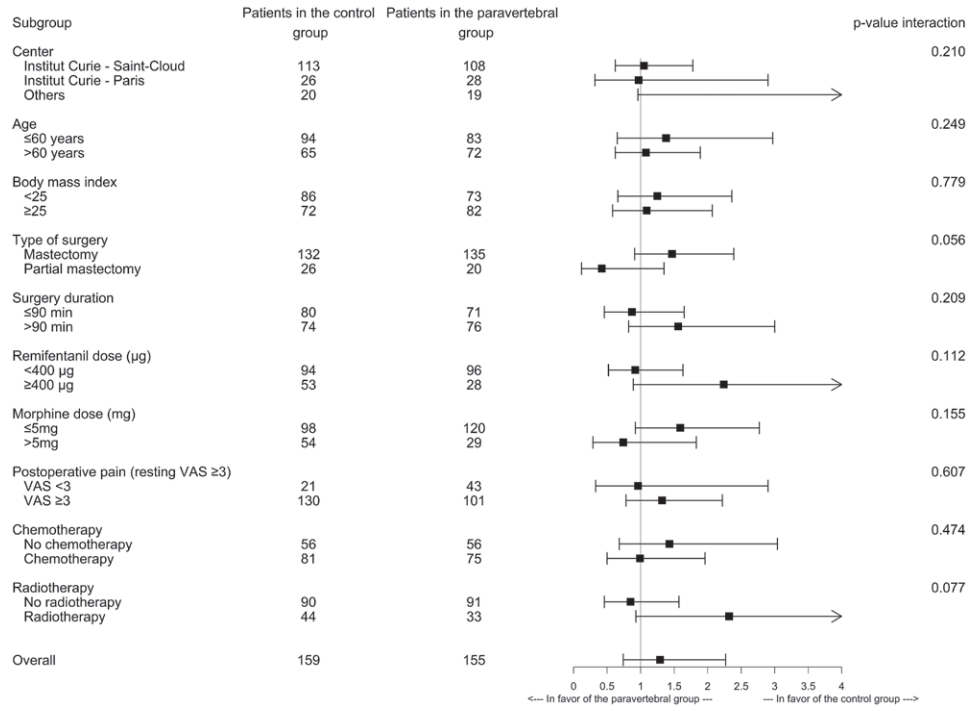

Fig. 3. Forest plot assessing the effects of baseline factors in subgroups groups stratified by treatment (control group or paravertebral group) on chronic postoperative pain 3 months after breast surgery. These results were obtained from the per-protocol population; as for the primary endpoint, the patients with missing Brief Pain Inventory data at 3 months were considered to experience pain. Hazard ratios and interaction *P* values were assessed by logistic regression models. The data in this forest plot appear to show that the type of surgery could be associated with an effect on pain at 3 months depending on the treatment received (interaction *P* value = 0.056). Pain at 3 months tended to be less common in the control group in the case of complete mastectomy, whereas pain tended to be less common in the paravertebral group in the case of partial mastectomy, but the difference is not statistically different. VAS, visual analogue scale.

scores alone and confirmed the absence of a difference in pain and its impact on quality of life.

Acute postoperative pain scores, remifentanil doses during surgery, and morphine consumption in the first 2 postoperative hours were lower in the paravertebral block group than in the control group in our study. One previous study found that a significantly lower pain score in the first 2 h after breast surgery with paravertebral block was associated with a significantly lower consumption of opioids compared to control.[15] In a meta-analysis, there was conclusive evidence that paravertebral block led to a clinically relevant reduction in acute pain (VAS score greater than 1), 24-h morphine consumption, and incidence of nausea and vomiting (greater than or equal to 25% relative reduction). However, the quality of evidence was downgraded to moderate or low due to the lack of adequate blinding and the high degree of heterogeneity across trials, mainly due to differences in baseline analgesia.[4] In our study, this reduction in acute pain and opioid consumption did not persist after the PACU period, and lower opioid consumption did not reduce the incidences of nausea, vomiting, or chronic pain. Therefore, although paravertebral block provided a short-term benefit after breast cancer surgery, unlike in other studies, no long-term benefit was identified with this technique in our study.[2,15]

The risk factors for persistent postoperative pain can be related to the patient and the quality of analgesia, surgery, and cancer treatments.[16,17] Patients at risk of severe postoperative pain (preoperative chronic pain, a reported history of substance abuse or opioid treatment) were not included in our study. Subgroup analyses were performed to detect any subgroups in which a beneficial effect could be observed, but we did not find any significant difference between these subgroups (fig. 3). Although the difference in VAS score for acute pain was significant between the two groups during the first 2 postoperative hours but not associated with a difference in the incidence of chronic pain, the mean VAS scores at rest and during mobilization after the first 2 postoperative hours were less than 2 in both groups. This is considered to be sufficient pain relief after surgery. Notably, low pain scores reduce the likelihood of detecting a significant difference in chronic pain between groups. Our study showed that paravertebral block did not reduce the incidence of chronic pain in patients who underwent partial or complete mastectomy (fig. 3). Although two earlier studies showed that paravertebral block reduces

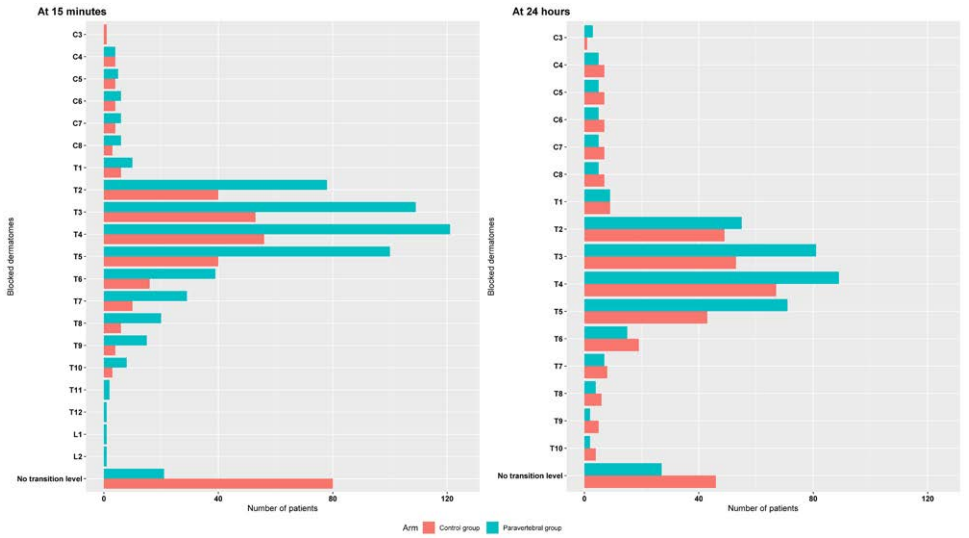

Fig. 4. Blocked dermatomes 15 min and 24 h after an injection of ropivacaine or saline in the paravertebral space in the paravertebral group and control group, respectively. Evaluations of blocked dermatomes were performed through cold ice tests; at 15 min, significantly more patients had at least one dermatome blocked in the paravertebral group than in the control group (84.8% [95% CI, 77.7 to 90.3] *vs.* 43.7% [95% CI, 35.4 to 52.2]; $P < 0.001$). At 24 h, the difference between the two groups concerning blocked dermatomes was still observed, although it was less marked (78.2% [95% CI, 69.9 to 85.1] *vs.* 64.9% [95% CI, 56.1 to 73.0]; $P = 0.019$).

the incidence of chronic pain after partial mastectomy,[11,12] the results regarding complete mastectomy are more conflicting. The breast and chest wall are innervated by a combination of thoracic intercostal (1 to 7), brachial plexus, and superficial cervical plexus nerves. The cephalad part of the breast also receives some innervation from the supraclavicular nerves (superficial cervical plexus). The pectoralis major and minor muscles, as well as their fascia, are supplied by the medial and lateral pectoral nerves. The axilla exhibits complex innervation with a large contribution from the intercostobrachial nerve. While paravertebral block generally results in an ipsilateral blockade of the intercostal and sympathetic nerves, it does not block the supraclavicular nerves, pectoral nerves, or other brachial plexus branches. Therefore, paravertebral block may be insufficient for major breast surgery, especially for deep anatomical structures (pectoralis major and its fascia).[18,19]

The clinical effect of paravertebral block was confirmed by sensory blockade tests. Loss of cold sensation was evaluated 15 min after the block, which corresponded to the onset of ropivacaine. The extent of the loss of cold sensation was similar to that published in a previous study and covered the operative site (thoracic intercostal nerves 1 to 6) after a single injection.[20] Eighty-five percent of the patients in the paravertebral group experienced loss of cold sensation 15 min after the injection in the paravertebral space, and 92% experienced loss of cold sensation either 15 min or 24 h after the injection (fig. 4).

After 24 h, the loss of cold sensation persisted in 78% of the patients in the paravertebral group, with a reduction in the lower dermatome blockade from the sixth thoracic intercostal nerve to the fifth (fig. 4). There are very few studies that have reported unsuccessful sensory blockade, with an incidence of approximately 10%, which is similar to our results.[21,22] It is interesting to note that in the control group, 44% of patients reported that they had loss of cold sensation at 24 h. This result is difficult to evaluate because some nerves may have been injured during surgery. Forty-two percent of the patients in the control group also experienced loss of cold sensation after a paravertebral saline injection. This may be explained by a placebo effect or a false-positive response due to the patients' difficulty in evaluating this loss, even when comparing sensations to a reference cold sensation at the third cervical dermatome. This may also be the effect of the saline solution injection, which was found to be more painful in this group (table 1). The injection of liquid into closed spaces is painful (5 to 10% of patients), and patients can feel pressure in the chest. The incidence of pain is higher when the concentration of the injected ropivacaine is lower, which may explain the difference in pain intensity during the injection between the paravertebral block (ropivacaine 0.75%) and control groups.[23] The injection of saline solution into a closed space and resulting pain may have a transitory effect on nerve sensitivity, explaining the loss of cold sensation. After locoregional analgesia, evaluations of sensory block-extension can be difficult and are probably a limitation in these studies.[20]

Compared to previous studies, the current study includes a large number of patients, making it possible to detect small differences between groups, and different sites allowing

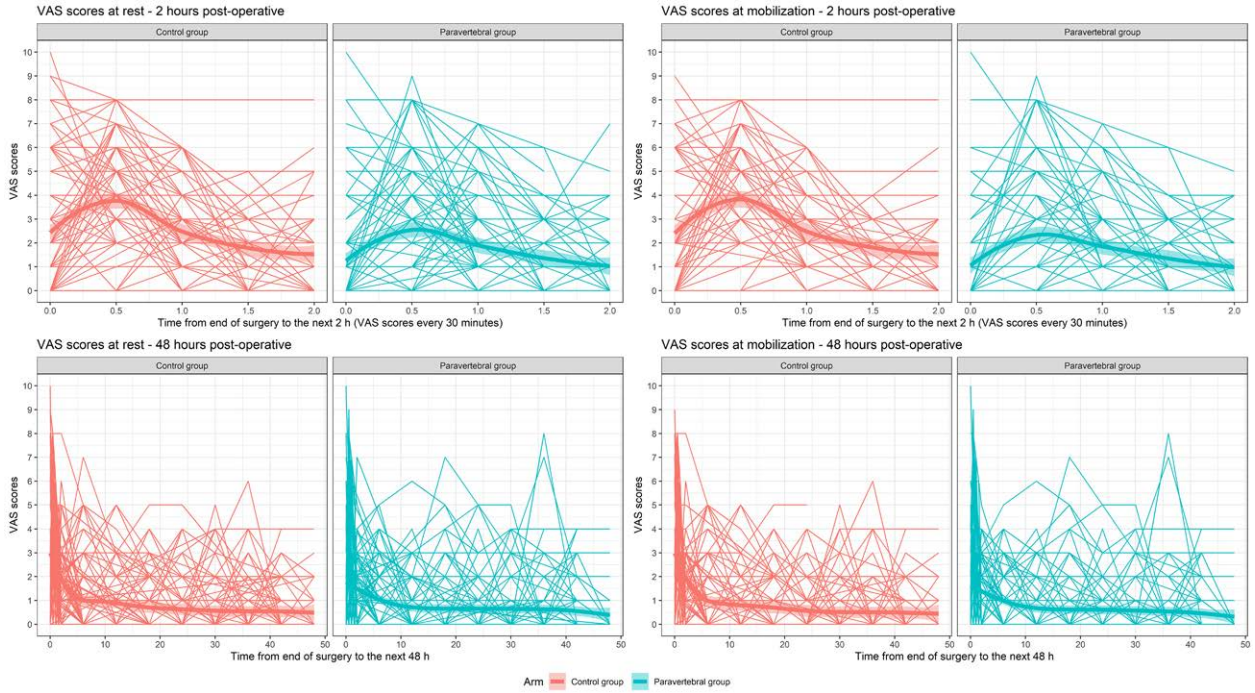

Fig. 5. VAS scores at rest and during mobilization during the first 2 postoperative hours and 48 postoperative hours. In the first 2 postoperative hours, both groups had a maximum pain score approximately 30 min after surgery both at rest and during mobilization. This maximum pain score was higher in the control group than in the paravertebral group. At rest, the mean VAS score at 30 min was 3.8 ± 2.1 in the control group and 2.5 ± 2.5 in the paravertebral group ($P < 0.001$). During mobilization, the mean VAS score at 30 min was 4.0 ± 2.2 in the control group and 2.4 ± 2.5 in the paravertebral group ($P < 0.001$). The AUCs reflects the intensity and duration of mean pain over the first 2 h. A comparison of AUCs between the two groups showed that the pain at rest was greater in the control group (4.3 ± 2.8 VAS score units × hours) than in the paravertebral group (2.9 ± 2.8 VAS score units × hours; $P < 0.001$). For pain during mobilization, the AUCs were 3.7 ± 3.2 in the control group *versus* 2.5 ± 2.5 VAS score units × hours in the paravertebral group ($P < 0.001$). After the first 2 postoperative hours and over the next 46 h, there was no difference in pain between the two groups at rest or during mobilization. AUC, area under the receiver operating characteristics curve; VAS, visual analogue scale.

for generalization of the results. We also provided long-term monitoring of pain with numerous validated tools. Moreover, our study, unlike others, compared the treatment group to a control group that received a saline injection in the paravertebral space, evaluated the results according to type of surgery (complete or partial mastectomy, sentinel or axillary lymph node dissection) and paravertebral block technique (one-level single thoracic puncture under ultrasound guidance), and specifically determined the blocked dermatomes.

Conclusions

Paravertebral block did not reduce the incidence of chronic pain after breast surgery. Paravertebral block did result in less immediate postoperative pain, but there were no other significant differences in postoperative outcomes.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

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Appendix

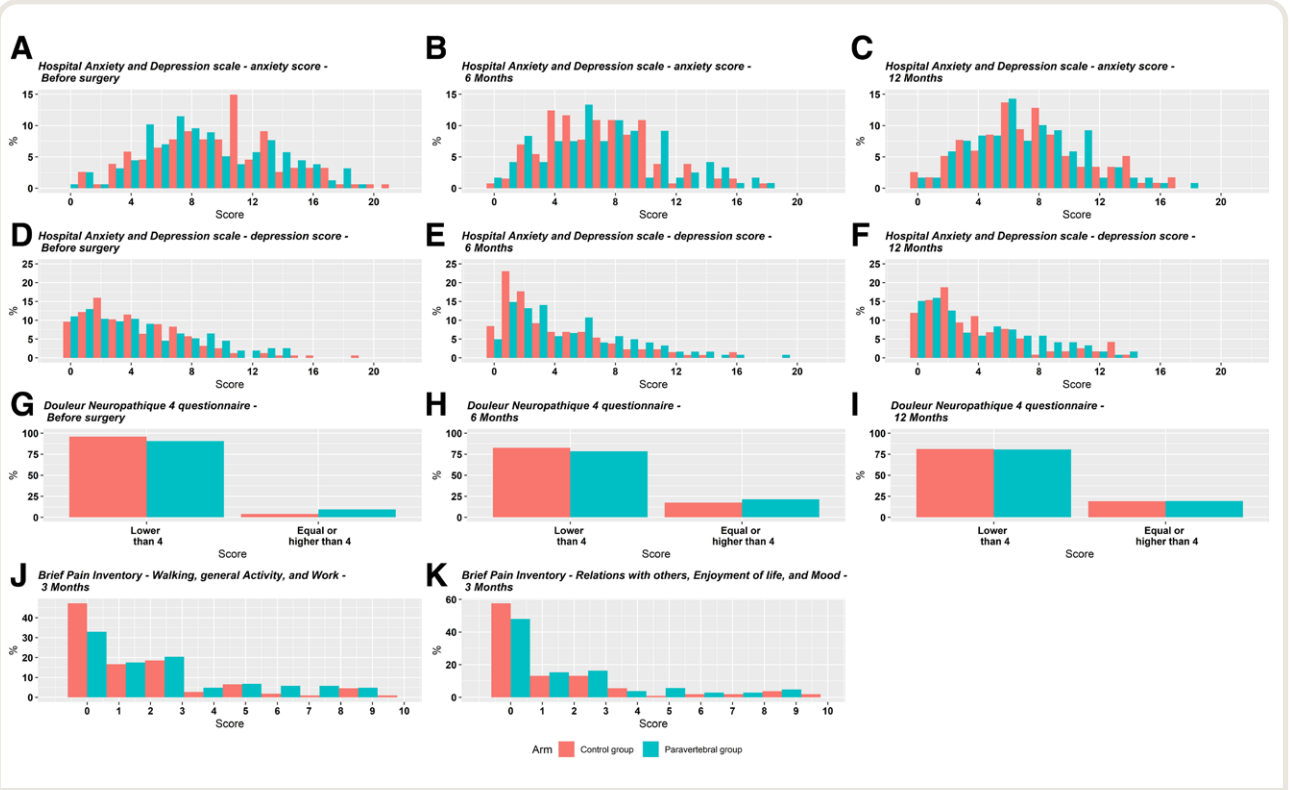

Fig. A1. Secondary endpoints: (*A–C*) Hospital Anxiety Depression Scale-anxiety scores, before surgery and at 6 and 12 months. (*D–F*) Hospital Anxiety Depression Scale-depression scores, before surgery and at 6 and 12 months. (*G–I*) Douleur Neuropathique 4 scores, before surgery and at 6 and 12 months. (*J*) Brief Pain Inventory subscale: Walking, general Activity, and Work scores 3 months after surgery. (*K*) Brief Pain Inventory subscale: Relations with others, Enjoyment of life, and Mood scores 3 months after surgery. Percentages are the percentage of patients for each score.

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Perioperative Pregabalin and Intraoperative Lidocaine Infusion to Reduce Persistent Neuropathic Pain After Breast Cancer Surgery: A Multicenter, Factorial, Randomized, Controlled Pilot Trial

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Abstract: **Persistent postsurgical pain is defined as pain localized to the area of surgery of a duration of ≥2 months and is, unfortunately, a common complication after breast cancer surgery. Although there is insufficient evidence to support any preventative strategy, prior literature suggests the possible efficacy of intravenous lidocaine and perioperative pregabalin in preventing persistent pain after surgery. To determine feasibility of conducting a larger definitive trial, we conducted a multicenter 2 × 2 factorial, randomized, placebo-controlled pilot trial of 100 female patients undergoing breast cancer surgery. Patients were randomized to receive an intraoperative lidocaine infusion (1.5 mg/kg bolus followed by 2 mg/kg/h) or placebo and perioperative pregabalin (300 mg preoperatively, 75 mg twice daily for 9 days) or placebo. All feasibility criteria were surpassed; recruitment of 100 patients was accomplished within 42 weeks, with a follow-up rate of 100% and study drug compliance of ≥80%. At 3 months, 53% of patients reported persistent neuropathic pain. Although there was no interaction between lidocaine and pregabalin, lidocaine decreased the development of persistent neuropathic pain (43.1% vs 63.3%; relative risk = .68; 95% confidence interval = .47–1.0).**

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Pregabalin did not reduce persistent pain (60% vs 46%; relative risk = 1.3; 95% confidence interval = .90−1.90) and neither pregabalin nor lidocaine impacted acute postoperative pain, opioid consumption, pain interference, or quality of life. Our pilot trial successfully demonstrated feasibility and provided promising data for conducting further trials of intraoperative lidocaine infusions during breast cancer surgeries.

Clinical trial number: NCT02240199

Perspective: ***This article reports the findings of a pilot randomized, controlled trial evaluating the effects of perioperative pregabalin and intraoperative lidocaine infusions in patients undergoing breast cancer surgery. This trial demonstrated the feasibility of conducting a larger trial and provided promising data that these interventions may decrease the development of persistent pain.***

Key Words: *Perioperative, pain, acute pain, chronic pain, surgery, clinical trial.*

Breast cancer is the most commonly diagnosed cancer among women and accounts for approximately 29% of annual new cancer cases worldwide.[42] Advances in screening and management have substantially improved the prognosis of breast cancer such that the 5-year survival rate exceeds 90%.[24] Improvement in mortality rates among patients with breast cancer have led to an increased focus on morbidity.

A central component of breast cancer management is surgical resection. Surgery includes resection of the presumed cancerous tissue with a sentinel lymph node biopsy for staging. If there is evidence of lymphatic spread, an axillary lymph node dissection is considered. Unfortunately, after breast cancer surgery, persistent pain is a common and disabling complication.[51] The International Association for the Study of Pain defines persistent pain after surgery as pain that develops due to a surgical procedure and is of ≥2 months in duration.[29] The median prevalence of persistent pain after breast cancer surgery is 38% at a median follow-up of 24 months.[51] Pain is typically located in the chest wall, axilla, and/or medial arm on the ipsilateral side of surgery and can arise from a multitude of causes, including cancer recurrence, infection, lymphedema, and neuropathic pain.[25] Although organic causes of pain should be ruled out, persistent neuropathic pain after surgery is likely triggered by peripheral nerve injury from surgical dissection and postoperative inflammation.[13] Postoperative chemotherapy and radiation have also been shown to contribute to the development of persistent pain.[5] Although breast cancer resection is performed via a mastectomy or lumpectomy, there seem to be similar rates of persistent pain across these surgical subgroups.[20,21,46,51]

Lidocaine is an amide local anesthetic that binds to the intracellular alpha-subunit of voltage-gated sodium channels.[35] Because pain transmission relies heavily on the functioning of sodium channels, lidocaine has a dose-dependent suppression of nerve conduction, decreasing the discharge rate of nociceptive afferent fibers, and causes suppression of specialized pain neurons after acute injury.[30] Lidocaine has been identified through various animal models to suppress spontaneous ectopic discharges, which may explain its beneficial effect in various neuropathic pain syndromes.[1,10,14] A recent systematic review (2 randomized trials, 97 patients) demonstrated a significant reduction of persistent pain after breast cancer surgery with the use of a perioperative lidocaine infusion (relative risk [RR] = .33; 95% confidence interval [CI] = .14−.78).[11] However, the included trials were small and were not able to demonstrate an effect on acute pain outcomes and other multidimensional effects of pain such as quality of life.

Pregabalin is a potent inhibitor of the alpha-2-delta subunit of voltage-gated calcium channels located in the central nervous system.[19] It was initially developed for epilepsy, but has been approved for the treatment of postherpetic neuralgia, diabetic peripheral neuropathy, and general anxiety disorder.[3,18] A 2013 Cochrane review (4 randomized trials, 439 patients) suggested a possible effect of perioperative pregabalin in reducing chronic postsurgical pain (RR = .70; 95% CI = .38−.95); this observation, however, was weighted by a small but strongly positive cardiac surgery trial.[12] A review conducted by our group of randomized trials restricted to breast cancer surgeries found no significant effect of gabapentinoids in reducing persistent pain.[37] Overall, there is uncertainty as to whether pregabalin has an effect on decreasing persistent pain after breast cancer surgery.

A large, high-quality, randomized, controlled trial is needed to establish the effects of pregabalin and lidocaine within a breast surgery context. However, before undertaking a definitive trial, we need to establish trial feasibility.[47] The primary purpose of this study was to determine the feasibility of conducting a larger randomized trial that will seek to determine independent effects of intravenous lidocaine and perioperative pregabalin. We used a factorial study design which allows for efficient and simultaneous investigation of 2 separate interventions, while allowing for detection of possible synergism.[7,34] We undertook a multicenter factorial randomized placebo-controlled pilot trial to assess the efficacy of intraoperative intravenous lidocaine infusion versus placebo and perioperative pregabalin versus placebo on the development of persistent pain after breast cancer surgery.

Methods

The methods of the study are reported according to the CONSORT guidelines, including amendments for reporting of factorial trials.[15,40] This trial was approved by the ethics review boards at Sunnybrook Health

Sciences Centre and Juravinski Hospital, respectively. Before patient enrollment, this trial was registered at clinicaltrials.gov (NCT02240199, Dr. PJ Devereaux/Dr. James Khan, September 15, 2014).

Trial Design

This multicenter, 2 × 2 factorial, randomized, placebo-controlled pilot trial was conducted at 2 Canadian hospitals (Juravinski Hospital and Cancer Centre; Sunnybrook Health Sciences Centre) between December 2014 and October 2015. Centers obtained ethics approval before starting recruitment. The Population Health Research Institute was the trial coordinating center and was responsible for the randomization process, data maintenance, data validation, analyses, and study coordination.

Sample Size

The sample size of the pilot trial was chosen to be 100 patients. This number was based on a size that would provide ample information in designing and planning the definitive trial.[47] The observed mean and standard deviation of the development of persistent pain at 3 months in the pilot trial would be used in sample size calculations for the larger trial. Previous authoritative papers on pilot trials suggested a sample size of ≥55 to estimate a standard deviation to be used in a sample size calculation for the full trial.[43] Thus, we chose to include 100 patients, which would provide sufficient data to meet all our objectives.

Patient Selection

Eligible patients were female, aged 18–75 years, undergoing a unilateral or bilateral mastectomy or lumpectomy for prophylaxis or belief of isolated cancerous lesions (biopsy suggestive of cancer or indeterminate) under general anesthesia. Patients were excluded if they met any of the following criteria: previous breast surgery within 6 months; undergoing a deep inferior epigastric perforators flap procedure; history of chronic pain or a chronic pain syndrome in the past 3 months; documented hypersensitivity or allergy to pregabalin, gabapentin, or lidocaine; history of ventricular tachycardia, ventricular fibrillation, atrioventricular block type II or III, or congestive heart failure; renal insufficiency (documented creatinine ≥120 μmol/L); known or previously documented cirrhosis; pregnant; unable to swallow study medications; surgeon believes patient inappropriate for inclusion in the trial; unlikely to comply with follow-up (eg, no fixed address); language difficulties that would impede completion of questionnaires; or patient required gabapentin or pregabalin for a medical condition or has taken these medications daily during the week before randomization.

Procedures

Research assistants identified eligible patients by screening breast surgeons' clinic lists, preoperative assessment clinic lists, and operating room booking lists. Eligible patients were approached for informed consent and voluntary participation. Written informed consent was obtained from all included patients before randomization. Baseline questionnaires included the Pain Catastrophizing Scale[45] and the Amsterdam Preoperative Anxiety and Information Scale.[33]

We randomized patients the day before surgery using a centralized system using a computer-generated randomization scheme in a 1:1:1:1 allocation. Patients were randomized into the following groups: (1) active lidocaine/active pregabalin, (2) active lidocaine/placebo pregabalin, (3) placebo lidocaine/active pregabalin, (4) placebo lidocaine/placebo pregabalin. Pregabalin and pregabalin placebo medications were compounded into identical blinded gelatin capsules. Lidocaine and lidocaine placebo were dispensed in identical blinded 60-mL syringes. All drugs were prepared and dispensed by the central pharmacy at each clinical site. The computerized system randomized patients in permuted blocks, stratifying for center and mastectomies with reconstruction. Stratification ensures that the treatment and control groups are similar with respect to known prognostic factors. We stratified for mastectomies with reconstruction given the low frequency of these procedures and previous report documenting their increased risk of persistent pain above mastectomies and lumpectomies.[50] Further, we stratified across recruitment centers given the potential for an unequal distribution of patients across centers and variations in practice that could influence study outcomes.[41] Our computerized randomization system alerted the central pharmacy on the next enrolled patient according to a unique ID. The pharmacy prepared the appropriate drug or placebo medications in their blinded capsules and syringes and provided them to the research assistant on the day of surgery. Research assistants provided the blinded preoperative pregabalin medication to the patient and the blinded lidocaine syringe to the attending anesthesiologist. As such, all patients, clinicians, data collectors, outcome assessors, and analysts were all blinded to group assignments.

Enrolled patients received pregabalin 300 mg or placebo within 30–120 minutes before surgery and then received pregabalin 75 mg or placebo twice a day for 9 days after surgery. This regimen was chosen based on previous studies using a 300-mg preoperative dose,[9] a 75-mg twice a day postoperative dose,[36] and extending the duration of treatment to several days after surgery.[9,17,36] Lidocaine or placebo was administered with anesthetic induction using a 1.5-mg/kg bolus followed by a 2.0-mg/kg/h infusion until the start of surgical closure. Our chosen infusion regimen was informed by prior trials that evaluated lidocaine infusions for colorectal surgery and within a breast surgery context.[23,27,32] The use of any oral pre-emptive or preoperative analgesics (eg, such as preoperative acetaminophen, nonsteroidal anti-inflammatories) besides study medications were restricted. Further, we restricted any additional intravenous lidocaine as well as any neuraxial or regional anesthetic techniques, except local wound infiltration by the surgeon, which was restricted to 50 mg of bupivacaine.

Other analgesics such as steroids, ketamine, and opioids were left to the discretion of the attending anesthesiologist. Further, there were no restrictions on postoperative pain management.

Study research assistants followed up with patients immediately after surgery in the recovery room to collect acute postoperative data. Once patients were discharged, they were either called at home by a research assistant or followed up electronically using an electronic data capture system.

Study Outcomes

The aim of the pilot trial was to determine the feasibility of conducting a larger adequately powered randomized trial. Feasibility was assessed using the following criteria: recruitment of 100 patients in 52 weeks by 2 active recruitment centers; a follow-up rate of ≥90% at the 3-month follow-up visit; and ≥75% study drug compliance for both study drugs.

Secondary outcomes of the pilot trial are the primary outcomes of the larger definitive trial. These secondary outcomes aim to determine the efficacy of each single intervention alone and included persistent neuropathic pain at 3 months after surgery; acute postoperative pain using the numerical rating scale (NRS) at rest and with movement (abduction of arm to 90° on the ipsilateral side of surgery) in the morning and evening for postoperative days 1−3 and 9; postoperative opioid consumption in parenteral morphine equivalents for postoperative days 1−3, 9, and at 3 months; time in the postanesthesia care unit and length of hospital stay; sensory and affective components of pain using the Short Form McGill Pain Questionnaire-2; impairments in daily functioning owing to pain using the Brief Pain Inventory; quality of life using the Short Form 36 Physical and Mental Components; and adverse events. For patients included in the trial who underwent bilateral mastectomies, the outcome of persistent neuropathic pain was made if ≥1 surgical side met criteria. For other secondary outcomes such as pain intensities, patients were asked to report on the side of worse pain intensity.

Patients were evaluated at the 3-month follow-up for the development of persistent neuropathic pain, defined as meeting 3 criteria: 1) any pain at rest or with movement localized to the axilla, arm, shoulder, or chest wall on the side of surgery, 2) pain was present 3 months after surgery (outcome evaluated only at 3-month follow-up),[29] and 3) pain was neuropathic in nature based on the Douleur Neuropathique en 4 Interview (DN4-Interview; ie, ≥1 of burning, painful cold, or electric shocks, and ≥1 of tingling, pins and needles, numbness, and itching).[6] The DN4-interview was developed with the original DN4 questionnaire and does not rely on patient examination—a cut-off score of 3 indicated neuropathic pain (sensitivity of 78.0% and specificity of 81.2%).[6] The development of persistent neuropathic pain will be the primary outcome of the definitive trial.

We evaluated for adverse outcomes throughout the study period. Postoperatively, we evaluated for lidocaine toxicity, respiratory depression, postoperative nausea and vomiting, vasopressor/inotrope use, opioid overdose, and arrhythmias. Lidocaine toxicity was defined as the presence of arrhythmia, convulsions, respiratory failure, or hypotension/shock and treatment with a lipid emulsion (Intralipid, a local anesthetic toxicity reversal). Respiratory depression in the trial was defined as postoperative recovery room use of naloxone, nonrebreather oxygen facemask, or noninvasive ventilation. Opioid overdose was defined as response to administration of naloxone. At the 3-month follow-up, patients were evaluated for other serious adverse events such as mortality, stroke, myocardial infarction, congestive heart failure, infection, and reoperation. These outcomes were initially reported by the patient or their family members, which prompted an investigation into their electronic medical records for confirmation. Infections were defined as any surgical/wound infection, breast abscess, urinary, chest wall or respiratory, or other infection associated with a temperature change (>38°C or <36°C), heart rate of >90 beats per minute, and elevated white cell count (if taken for clinical reasons).

We assessed outcomes immediately after surgery in the recovery room and again on postoperative days 1−3 and 9, and at 3 months after surgery. If patients were not in the hospital, we followed up with them over the phone or using an automated computerized patient data collection platform. This platform was developed specifically for this trial by an independent third-party provider (InputHealth).

Statistical Analysis

Feasibility was analyzed according to our *a priori* feasibility criteria. Our recruitment target was 100 patients within 52 weeks of active recruitment across 2 simultaneously recruiting centers. Our follow-up target was a ≥90% follow-up rate at the 3-month follow-up visit. Finally, our study drug compliance target was a compliance rate of ≥75% throughout the study period for each drug.

The factorial design of the trial allowed for comparison of 2 separate interventions. Comparisons were made between patients who received active lidocaine to those who received placebo lidocaine, and between those who received active pregabalin and those who received placebo pregabalin. An analysis for interaction with the pregabalin and lidocaine combination was also performed. An analysis of efficacy outcomes was performed primarily for exploratory purposes given that the trial was not powered for hypothesis testing. All outcomes were described with the appropriate descriptive statistic (mean and standard deviation or median and interquartile range for continuous outcomes, or number and proportion for the categorical outcomes). Subgroup analyses were not performed owing to the small sample size of the trial. Analyses were performed according to an intention-to-treat protocol. If there was missing data for persistent pain (ie, lost to follow-up at 3 months), patients will be identified as not having persistent pain, if there was >5% of missing data at 3 months; otherwise, no imputation would be performed.

A sensitivity analysis assuming the patients lost to follow-up did not have persistent pain will then be performed. All findings were considered significant at a *P* value of <.05. All analyses were performed using SAS software, version 9.4 for UNIX (Cary, North Carolina).

An analysis of the binary outcome of persistent neuropathic pain was performed using a generalized linear model for each drug group separately (ie, the model included only independent drug allocation). The model was then further adjusted by the other drug intervention and an interaction term was also added to the model to assess for potential synergism between lidocaine and pregabalin. Although previous data suggest an independent effect on reducing persistent pain after surgery with intravenous lidocaine and perioperative pregabalin, we did not expect synergism with the combination therapy of these 2 interventions. Risk was reported as a RR and 95% CI. A post hoc analysis of moderate to severe postmastectomy pain (NRS $\geq$ 4) was also performed.

Daily pain scores at rest and movement were determined by averaging morning and evening pain scores; a distinction was made between pain at rest and pain with movement because the literature suggests that treatments may have a differential impact on these types of pain.[44] A pain curve was developed by plotting pain scores for postoperative days 1–3 and 9 and 3 months after surgery. A linear mixed model with repeated measures was used to explore pain scores at rest and with movement over time between the treatment groups. The fixed effects were time, treatment, and interaction between time and treatment. We used an unstructured covariance matrix to account for the within-subject correlation. The least squares means for the scores at different times are presented and the pair-wise differences between the treatment groups reported (Tukey-adjusted *P* values). Opioid consumption in the recovery room and postoperatively was converted to parenteral morphine equivalents using an opioid analgesic conversion table.[4]

Categorical outcomes, such as adverse events, were reported using count and proportion and compared using χ^2 tests or Fisher's exact tests for small sample sizes. Continuous outcomes, such as time to recovery room or hospital discharge, Short Form McGill Pain Questionnaire-2, Brief Pain Inventory, and Short Form 36, were described using means and 95% CI or median and interquartile range and compared using the Student *t*-test or Wilcoxon 2-sample test if the normality assumption did not hold true.

Results

Of 296 eligible patients, 165 declined participation and 31 could not be contacted preoperatively for inclusion. A total of 100 patients were randomized; 51 patients were allocated to active lidocaine and 49 patients to placebo lidocaine, and 50 patients were allocated to active pregabalin and 50 patients to placebo pregabalin. All patients completed the trial follow-up, and all patients were included in the secondary analyses (Figure 1).

Table 1 shows the baseline characteristics overall and for the lidocaine and pregabalin groups. The average

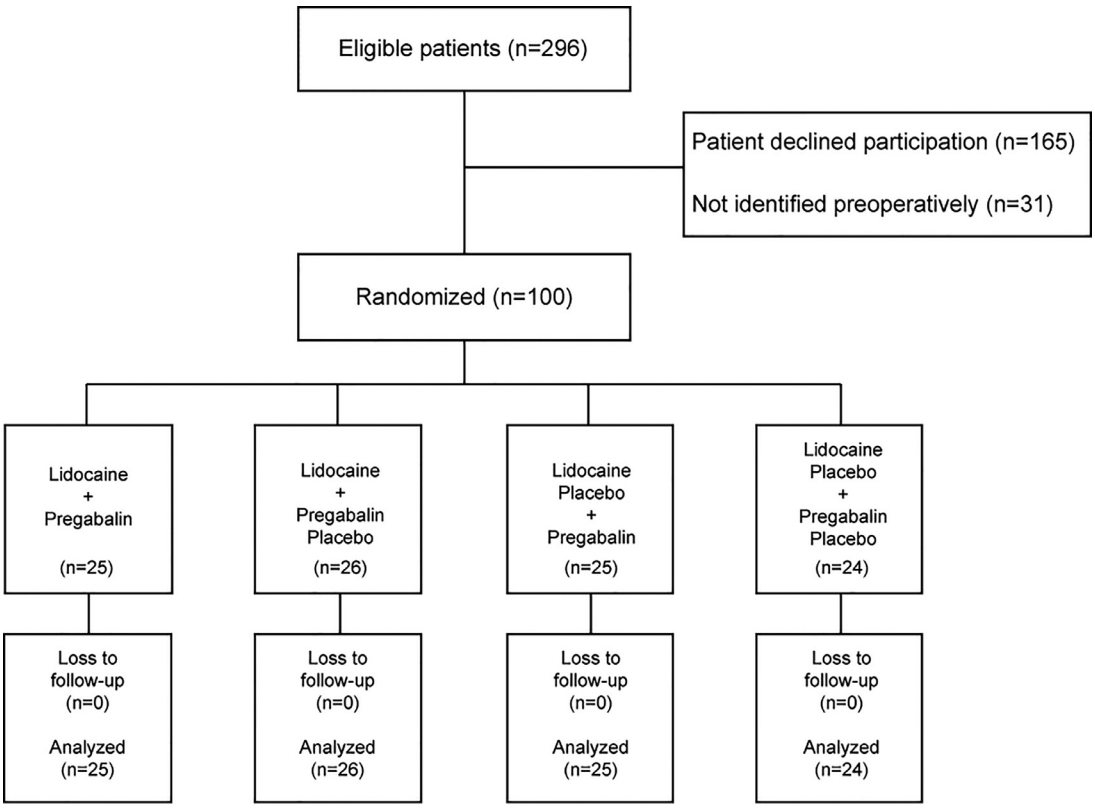

Figure 1. Patient study flow diagram.

Table 1. Baseline Characteristics

	Overall (N = 100)	Active Lidocaine (N = 51)	Placebo Lidocaine (N = 49)	Active Pregabalin (N = 50)	Placebo Pregabalin (N = 50)
Age, y, mean (SD)	54.3 (11.1)	55.2 (11.6)	53.4 (10.5)	54.2 (9.5)	54.4 (12.5)
Weight, kg, mean (SD)	76.9 (19.5)	74.7 (20.6)	79.2 (18.2)	80.0 (22.7)	73.7 (15.3)
Diabetes, n (%)	7 (7.0)	4 (7.8)	3 (6.1)	2 (4.0)	5 (10.0)
Current smoker, n (%)	10 (10.0)	4 (7.8)	6 (12.2)	6 (12.0)	4 (8.0)
Reason for breast surgery					
Breast cancer/suspected cancerous lesions, n (%)	94 (94.0)	49 (96.1)	45 (91.8)	47 (94.0)	47 (94.0)
Prophylactic, n (%)	6 (6.0)	2 (3.9)	4 (8.2)	3 (6.0)	3 (6.0)
Preoperative chemotherapy, n (%)	13 (13.0)	5 (9.8)	8 (16.3)	5 (10.0)	8 (16.0)
Preoperative radiation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Previous breast cancer, n (%)	10 (10.0)	3 (5.9)	7 (14.3)	6 (12.0)	4 (8.0)
Type of procedure, n (%)					
Bilateral lumpectomy	1 (1.0)	1 (2.0)	0 (0.0)	1 (2.0)	0 (0.0)
Bilateral mastectomy	6 (6.0)	2 (3.9)	4 (8.2)	2 (4.0)	4 (8.0)
Unilateral lumpectomy	75 (75.0)	40 (78.4)	35 (71.4)	36 (72.0)	39 (78.0)
Unilateral mastectomy	18 (18.0)	8 (15.7)	10 (20.4)	11 (22.0)	7 (14.0)
Axillary node dissection, n (%)	7 (7.0)	4 (7.8)	3 (6.1)	4 (8.0)	3 (6.0)
Sentinel node biopsy, n (%)	63 (63.0)	33 (64.7)	30 (61.2)	33 (66.0)	30 (60.0)
Intraoperative medications					
Fentanyl, μg, mean (SD)	137.9 (83.0)	122.7 (59.1)	156.5 (103.4)	123.1 (57.0)	148.3 (96.7)
Morphine, mg, mean (SD)	7.3 (1.7)	5 (5.0)	8.0 (1.0)	8.0 (1.4)	6.5 (2.1)
Hydromorphone, mg, mean (SD)	.71 (.3)	.65 (.31)	.80 (.28)	.79 (.33)	.62 (.25)
Ketamine, mg, mean (SD)	15 (5.0)	0 (.0)	15 (5.0)	10 (.0)	17.5 (3.5)
Dexamethasone, mg, mean (SD)	6.4 (2.0)	6.4 (2.2)	6.4 (1.9)	6.1 (1.9)	6.7 (2.2)
Ketorolac, mg, mean (SD)	25.0 (7.3)	25.0 (7.5)	25.0 (7.7)	26.3 (6.9)	23.6 (8.0)
Implants placed, n (%)	1 (1.0)	0 (.0)	1 (2.0)	0 (.0)	1 (2.0)
Periareolar incision, n (%)	1 (1.0)	1 (2.0)	0 (.0)	0 (.0)	1 (2.0)
Fat grafts used, n (%)	4 (4.0)	2 (3.9)	2 (4.1)	2 (4.0)	2 (4.0)
Local wound infiltration, n (%)	64 (64.0)	35 (68.6)	29 (59.2)	30 (60.0)	34 (68.0)
Wound drains placed, n (%)	23 (23.0)	11 (21.6)	12 (24.5)	13 (26.0)	10 (20.0)
Pan Catastrophizing Score	11.9 (9.4)	11.1 (9.3)	12.8 (9.4)	11.1 (9.3)	12.8 (9.4)
APAIS: Anxiety component	8.99 (3.89)	8.90 (3.96)	9.08 (3.85)	8.90 (3.96)	9.08 (3.85)

Abbreviations: SD = standard deviation; APAIS = Amsterdam Preoperative Anxiety and Information Scale.

age of patients was 54.3 years (standard deviation = 11.1). The most common surgical procedure was unilateral lumpectomy (75%) followed by unilateral mastectomy (18%); the remaining 7% of patients underwent either a bilateral lumpectomy or mastectomy. The majority of patients (94%) underwent surgery for suspected cancerous lesions; 6 patients had surgery for prophylactic mastectomies. Sixty-three percent of patients had a sentinel lymph node biopsy and only 7% had an axillary node dissection.

Feasibility

Our recruitment target was to recruit 100 patients across 2 actively recruiting centers within a total of 52 weeks of active recruitment. Recruitment started in December 2014 and trial recruitment finished in October 2015. Our recruitment target was met after 42 weeks.

We met our follow-up target with a 100% follow-up rate at 3 months. However, 2 patients did not complete the postoperative day 1–3 and 9 visits, and 1 patient refused to complete the postoperative day 9 visit. This provided a 98% follow-up rate for the acute postoperative data.

We aimed to achieve a study drug compliance rate of ≥75% with both lidocaine/placebo and pregabalin/placebo study medications. Ninety-two patients (92%) received lidocaine or placebo intraoperatively; 5 patients in the active lidocaine group and 3 patients in the placebo lidocaine group did not receive study medications. Reasons for not receiving lidocaine or placebo were anesthesiologist refusal (4 patients), anesthesiologist forgot (1 patient), limited time to setup infusion (1 patient), patient refusal at time of surgery (1 patient), and unclear whether study drug was administered (1 patient). None of the lidocaine infusions were stopped prematurely. Compliance with pregabalin or placebo was >88% throughout the perioperative period. Preoperative pregabalin and placebo compliance was 98%. Postoperatively, placebo pregabalin had a compliance rate of ≥92% during the 9 postoperative days; however, active pregabalin had a steady decline in compliance to 80% on postoperative day 9 (Supplementary Table 1). The most common reasons for not taking pregabalin study medications were mild side effects, refusal, or patient losing the study medications (Supplementary Table 2).

Table 2. Persistent Neuropathic Pain, SF-MPQ II, BPI, and SF-36 Scores at the 3-Month Follow-up Visit

	Active Lidocaine (N = 51)	*Placebo Lidocaine (N = 49)*	P *Value*	*Active Pregabalin (N = 50)*	*Placebo Pregabalin (N = 50)*	P *Value*
Persistent neuropathic pain, n (%)	22 (43.1)	31 (63.3)	.049*	30 (60.0)	23 (46.0)	.166
Moderate to severe persistent neuropathic pain,† n (%)	4 (7.8)	8 (16.3)	.205	6 (12.0)	6 (12.0)	1.000
SF-MPQ II, median (Q1–Q3)	26.0 (22.0–37.0)	29.0 (24.0–48.0)	.209	27.0 (23.0–50.0)	28.0 (22.0–43.0)	.725
BPI, median (Q1–Q3)						
General activity	1.0 (1.0–3.0)	1.0 (1.0–2.0)	.911	1.0 (1.0–2.0)	1.0 (1.0–3.0)	.885
Mood	1.0 (1.0–2.0)	1.0 (1.0–2.0)	.604	1.0 (1.0–2.0)	1.0 (1.0–3.0)	.774
Walking ability	1.0 (1.0–1.0)	1.0 (1.0–2.0)	.444	1.0 (1.0–1.0)	1.0 (1.0–1.0)	.1.0
Normal work	1.0 (1.0–3.0)	1.0 (1.0–3.0)	.809	1.0 (1.0–2.0)	1.0 (1.0–3.0)	.669
Relationships	1.0 (1.0–1.0)	1.0 (1.0–1.0)	.648	1.0 (1.0–1.0)	1.0 (1.0–1.0)	.521
Sleep	1.0 (1.0–4.0)	1.0 (1.0–3.0)	.724	1.0 (1.0–4.0)	1.0 (1.0–3.0)	.962
Enjoyment of life	1.0 (1.0–3.0)	1.0 (1.0–4.0	.517	1.0 (1.0–3.0)	1.0 (1.0–4.0)	.379
SF-36 PCS, median (Q1–Q3)	45.6 (36.6–54.6)	44.9 (37.7–55.1)	.535	45.5 (37.3–54.4)	45.6 (37.8–55.3)	.697
SF-36 MCS, median (Q1–Q3)	50.1 (41.2–56.1)	50.6 (40.8–57.2)	.710	50.4 (39.2–57.1)	50.3 (41.9–57.0)	.657

Abbreviations: BPI = Brief Pain Inventory; MCS = Mental Component Score; PCS = Physical Component Score; SF-36 = Short Form 36; SF-MPQ II = Short Form McGill Pain Questionnaire II; SD = standard deviation.
*$P < .05$.
NOTE.
†Clinically significant pain defined as persistent neuropathic pain with NRS of ≥4 of 10 at rest.

Efficacy

At the 3-month follow-up, 53% of patients had persistent neuropathic pain. At rest, approximately 77.4% of these patients suffered from mild pain (NRS of 0–3), 15.1% had moderate pain (NRS of 4–6), and 7.5% had severe pain (NRS of 7–10). On movement (abduction of arm on ipsilateral side of surgery), 69.8% of patients suffered mild pain, 17.0% moderate pain, and 13.2% severe pain. Lidocaine significantly decreased the development of persistent neuropathic pain (43.1% vs 63.3%; RR = .68, 95% CI = .47–1.0; $P = .049$; Table 2). Lidocaine, however, did not significantly decrease moderate to severe persistent neuropathic pain (NRS of ≥4), 7.8% versus 16.3% (RR = .48; 95% CI = .16–1.49; $P = .205$). Pregabalin did not significantly decrease persistent neuropathic pain (60% vs 46%; RR = 1.3; 95% CI = .90–1.90; $P = .166$) or moderate to severe persistent neuropathic pain (12% vs 12%; RR = 1.00; 95% CI = .35–2.89; $P = 1.00$). There was no interaction of combination lidocaine and pregabalin on reducing persistent pain (52% vs 58.3%; RR = .89; 95% CI = .54–1.48; $P = .656$).

There were no differences in pain scores at rest ($P = .295$) or with movement ($P = .220$) between lidocaine and placebo (Fig 2A and 2B), or between pregabalin and placebo ($P = .734$ for pain at rest; $P = .929$ for pain on movement; Fig 3A and 3B). There was no difference in opioid consumption over time between lidocaine and placebo ($P = .713$) or pregabalin and placebo ($P = .300$; Table 3). Neither lidocaine nor pregabalin affected SF-MPQ-II, Brief Pain Inventory Pain Interference, or Short Form 36 Physical or Mental Component Scores at 3 months (Table 2).

Times to recovery room and hospital discharge were similar in the lidocaine versus placebo and pregabalin versus placebo groups (Table 3 and Figure 4). With respect to adverse events, there were no documented cases of lidocaine toxicity in any patient. One patient who was in the placebo lidocaine/placebo pregabalin group had an episode of respiratory depression in the recovery room. This patient required the use of naloxone and no other therapies to improve ventilation, indicating likely opioid-induced respiratory depression. One patient in the active lidocaine/active pregablin group required the use of a vasopressor in the recovery room. Postoperative nausea was similar across treatment groups; however, postoperative vomiting was significantly higher in the pregabalin versus placebo group (12% vs 0%; $P = .027$; Table 3). The risk of infection was similar across groups and there were no documented cases of mortality, stroke, myocardial infarction, congestive heart failure, or arrhythmias. Further, there were no differences in rates of postoperative chemotherapy or radiation and none of the included patients required reoperation for recurrence of breast cancer, infection, breast implants/expanders, or other reasons within our study period.

Discussion

Invaluable insights gained from this pilot will aid in the design and conduct of the larger trial. We demonstrated that a factorial design trial evaluating 2 perioperative interventions to decrease persistent pain after surgery, with one being an oral medication and the other being an intravenous infusion, is a feasible study design. We have also determined recruitment rates in individual centers, found excellent adherence to study protocol and data collection procedures, achieved an excellent follow-up rate, and established patient compliance with treatment. These are promising data as we

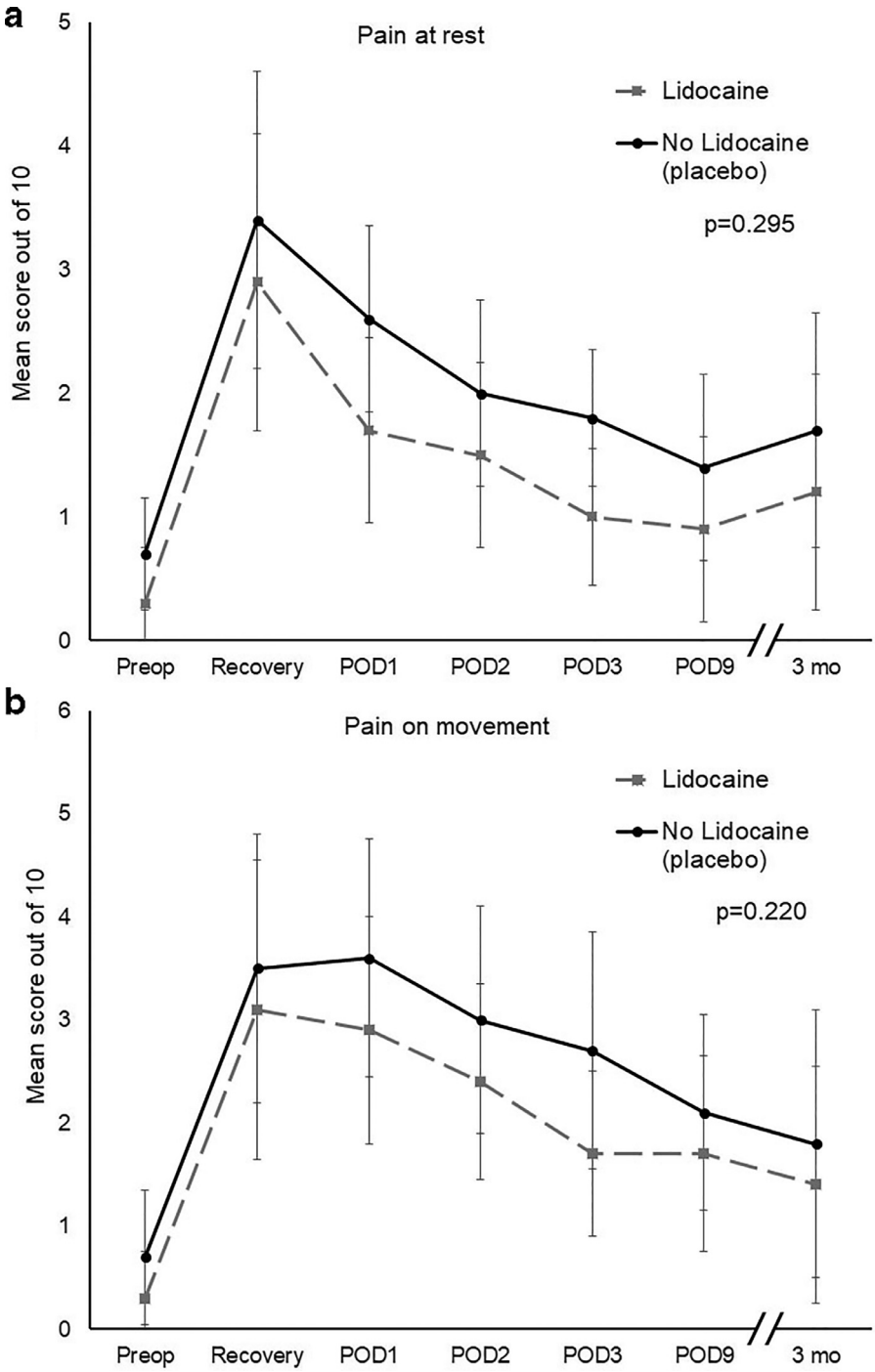

Figure 2. Time course of pain intensity, as assessed on a 0 to 10 NRS, per administration of intravenous lidocaine. POD = postoperative day.

look to conduct a larger definitive randomized trial with a similar study design.

We have also obtained encouraging data about the potential benefit of an intraoperative lidocaine infusion that warrants further investigation, and data regarding pregabalin that require further consideration on its efficacy and tolerability in the perioperative setting. Although recognizing the underpowered size of the pilot trial, our results suggest an effect with the use of an intraoperative intravenous lidocaine infusion on reducing persistent pain. Our findings are consistent with results from a recent meta-analysis of 6 studies (n = 420 patients) evaluating perioperative lidocaine infusions across noncardiac surgeries (4 breast cancer surgeries, 1 robotic thyroidectomy, open nephrectomy) on the development of chronic postsurgical pain.[2] In this review, perioperative lidocaine significantly reduced the incidence of chronic postsurgical pain (odds ratio = .29; 95% CI = .18−.48; I^2 = 0%). Furthermore, in a recent randomized trial of 150 patients undergoing breast cancer surgery, lidocaine infusion did reduce pain in the area of surgery by 16% (P = .04)

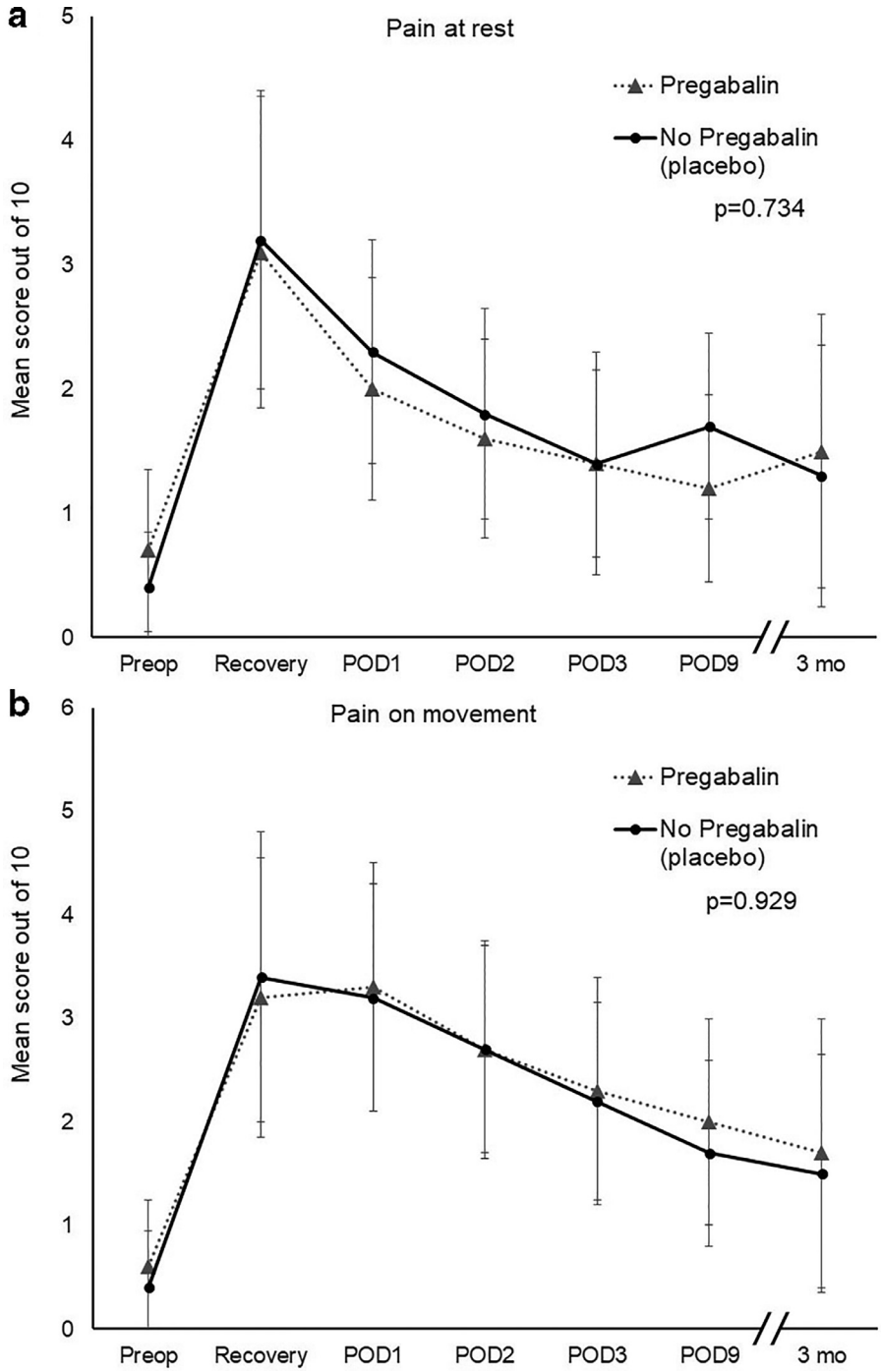

Figure 3. Time course of pain intensity, as assessed on a 0 to 10 NRS, per administration of oral pregabalin. POD = postoperative day.

at the 6-month follow-up; however, this study did not find any difference in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) criteria for persistent pain at 3 or 6 months.[26] Although these results add to an emerging body of literature in support of lidocaine infusions in breast cancer surgery, these studies are of small sample size or underpowered. A large, adequately powered trial is needed to definitively identify the beneficial effects of lidocaine infusions in a surgical breast cancer population. A larger trial will also allow for an evaluation at a longer follow-up (ie, 1 year) to potentially identify the duration of benefit of lidocaine, but also allow for subgroup analyses that could identify patients who would be high responders.

If lidocaine truly has an effect at reducing persistent pain after breast cancer surgery, it is interesting that these effects are well beyond the time required for plasma lidocaine levels to decrease to negligible levels (the half-life of lidocaine is 100 minutes).[38] Lidocaine's primary mechanism of action is the inhibition of voltage-gated sodium channels, and inactivation of sodium channels after peripheral nerve injury could interrupt the development of peripheral and central sensitization.[8]

Table 3. Postoperative Outcomes and Adverse Events

	Active Lidocaine (N = 51)	Placebo Lidocaine (N = 49)	P Value	Active Pregabalin (N = 50)	Placebo Pregabalin (N = 50)	P Value
Length of surgery, h, median (Q1–Q3)	1.0 (.8–1.4)	1.0 (.7–1.2)	.735	.9 (.8–1.2)	1.0 (.7–1.4)	.741
Recovery room, h, median (Q1–Q3)	1.0 (.9–1.3)	1.0 (.8–1.3)	.871	1.1 (.9–1.4)	1.0 (.8–1.3)	.079
H-LOS, d, median (Q1–Q3)	3.2 (2.4–4.9)	2.9 (2.4–16.5)	.901	3.2 (2.5–6.6)	2.8 (2.2–12.1)	.136
Lidocaine toxicity, n (%)	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Resp. depression, n (%)†	0 (0)	1 (2)	.49	0 (0)	1 (2)	1.0
Vasopressor/inotrope use, n (%)‡	1 (2)	0 (0)	1.0	1 (2)	0 (0)	1.0
Naloxone use, n (%)§	0 (0)	1 (2.0)		0 (0)	1 (2.0)	
Postoperative nausea, n (%)	10 (19.6)	11 (22.4)	.727	12 (24)	9 (18)	.461
Postoperative vomiting, n (%)	1 (2)	5 (10.2)	.108	6 (12)	0 (0)	.027*
All infections, n (%)	6 (11.8)	7 (14.3)	.708	6 (12)	7 (14)	.766
Surgical site infection, n (%)	4 (7.8)	3 (6.1)	1.0	4 (8)	3 (6)	1.0
All-cause mortality, n (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Stroke, n (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Myocardial infarction, n (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Congestive heart failure, n (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Arrhythmia, n (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Postoperative chemotherapy, n (%)	17 (33.3)	15 (30.6)	.771	20 (40.0)	12 (24.0)	.086
Postoperative radiation, n (%)	20 (39.2)	19 (38.8)	.964	15 (30.0)	24 (48.0)	.065

Abbreviation: H-LOS, hospital length of stay.
NOTE.
*$P < .05$.
†Respiratory depression was defined as postoperative recovery room use of naloxone, nonrebreather oxygen facemask, or noninvasive ventilation.
‡Defined as recovery room of any vasopressor or inotrope.
§Defined as recovery room use of naloxone.

Surgery induces neuronal injury and initiates the release of inflammatory mediators such as prostaglandins, serotonin, bradykinin, and epinephrine that sensitize local nociceptive terminals.[54] These sensitizing agents activate intracellular pathways that phosphorylate a tetrodotoxin-resistant sensory neuron–specific sodium ion channel, leading to its activation, changes in rate of activation/inactivation, and a decrease in threshold required to produce action potential.[54] This modulation leads to peripheral sensitization where there is a decrease in the threshold and amplification in responsiveness to nociceptive input.[28] Peripheral sensitization alone can contribute to the development of persistent pain, but ongoing peripheral nociceptive input can also lead to changes within the central nervous system, ultimately leading to central sensitization and features of allodynia and hyperalgesia.[28] Lidocaine also possesses a number of effects on key ion channels (eg, calcium and potassium channels) and receptors (eg, G protein-coupled, *N*-methyl-D-aspartate, and glycine receptors) involved in the pain pathway, as well anti-inflammatory properties.[16,30,49,53]

Although there was a trend for a decrease in postoperative opioid consumption with both interventions within the first 3 postoperative days, there was no significant difference over time found in the mixed model analysis. This finding is discordant with the literature, which suggests an opioid-sparing effect of both intravenous lidocaine and perioperative pregabalin.[22,37,52,55] This finding may relate to the underpowered size of the trial and that, for pregabalin, a relatively low dose was chosen. Furthermore, pregabalin did not have an effect on persistent opioid use or persistent neuropathic pain at 3 months after surgery. Although all the efficacy results of this trial must be viewed cautiously in light of the underpowered size of the trial, the finding of pregabalin's lack of effect on persistent postsurgical pain is emerging elsewhere in the literature. A recently published systematic review across all noncardiac and cardiac surgical procedures (15 randomized trials with a total of 1,884 patients) did not find any effect of pregabalin or gabapentin on reducing chronic postsurgical pain at 3 months after surgery (RR = .87; 95% CI = .66–1.14).[31] Further, a review specific to a patients undergoing surgery for breast cancer found no evidence to suggest a reduction in persistent pain with pregabalin.[37] Compliance rates seen in our trial with pregabalin had a sharp decline after postoperative day 5, which was reported to be due to side effects—pregabalin has known side effects such as somnolence, dizziness, and impairments in cognition.[39] In light of emerging data and tolerability with pregabalin, our investigative team will need to revisit inclusion of pregabalin in the larger definitive trial.

Our pilot trial suggests the safety of administering intraoperative intravenous lidocaine infusions in breast cancer surgery patients. Although a concern for toxicity exists with lidocaine, we did not have any documented cases and there were no documented serious adverse events with either lidocaine or pregabalin (Table 3). However, there was a decrease in the compliance with active pregabalin during the acute postoperative days (Supplementary Table 1) as well as an increase in postoperative vomiting in those who received pregabalin. This increase in vomiting, however, may be spurious given the small sample size and that it is discordant with

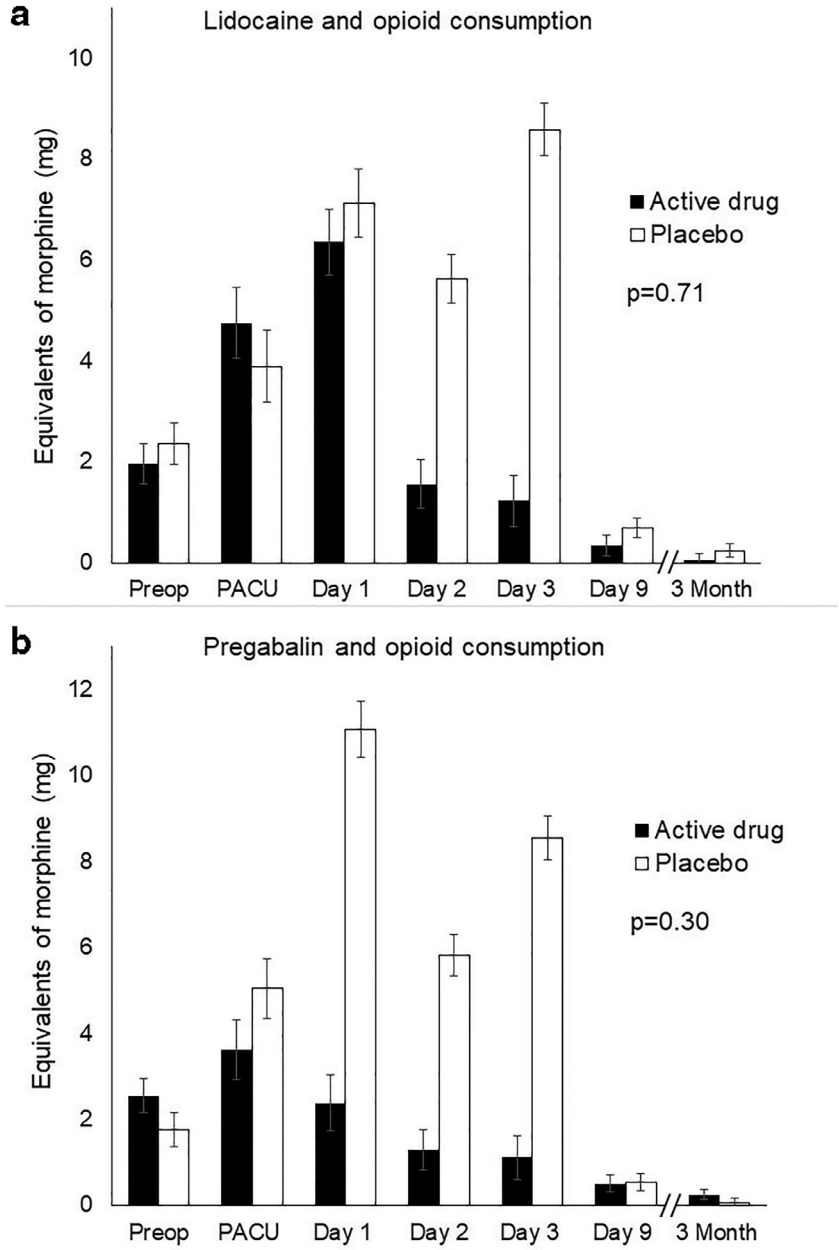

Figure 4. Time course of opioid consumption calculated in equivalents of parenteral morphine (milligrams), depending on the administration of intravenous lidocaine (top) and of oral pregabalin (bottom). PACU = postanesthesia care unit.

previous meta-analytical data[31,56] that suggest an antiemetic effect of pregabalin.

As we look forward to planning a larger randomized trial that will include intravenous lidocaine and possibly pregabalin, or another perioperative oral medication, in a factorial design, our pilot has provided data to inform sample size calculations, number of sites required, and expected costs. Using the lower limit of the 95% CI for the point estimate of persistent pain found in the pilot (38.3%) to identify a RR reduction of 25% of a single intervention, with 90% power and an alpha of .025 (.05 overall), the sample size of the larger trial will be approximately 1,200 patients. Given that on average we recruited 5 patients per month at each of the 2 recruiting sites, we would need 10 participating centers to successfully complete the larger trial in 2.0−2.5 years. Furthermore, the total cost of recruiting 100 patients into this pilot trial was approximately $150,000 CAD. The total cost of the full trial is estimated to be $1.8 million CAD.

The strengths of this pilot trial include a multicenter trial across 2 institutions, factorial design allowing for assessment of 2 perioperative interventions, and joint collaborations among anesthesiologists and surgeons allowing for the prompt and efficient recruitment of patients. Further, this trial obtained 100% follow-up at the 3 months, a success not common in trials examining preventive strategies for chronic postsurgical pain.[12]

Our study has several limitations. Given the small sample size of this trial, there was a high chance of imbalance of both known (ie, ketamine only received by lidocaine placebo patients in the lidocaine group) and

unknown prognostic factors. We also did not standardize the perioperative pain treatment of these patients. Attending physicians caring for enrolled study patients were able to administer pain medications as their own discretion—this was to improve generalizability and stratification by center would consider systemic differences in clinical care. Although randomization will balance this potential confounder, it could provide additional noise in the analyses. Further, 4% of patients in the pilot did not receive the lidocaine study medications owing to anesthesiologist refusal. The administration of lidocaine relied on the attending anesthesiologist delivering a bolus dose and setting up an infusion pump with a prespecified infusion dosage. This additional task may have led to our decreased compliance in lidocaine administration and we will implement strategies to improve this in the larger trial. Additionally, our lidocaine infusion regimen was limited to the intraoperative period. If in fact lidocaine decreases the peripheral and central sensitization that occurs in response to neural injury and inflammation, an extended duration of lidocaine beyond the operating room could provide greater benefit. Another limitation includes relying on a patient interview to determine persistent neuropathic pain. Although the DN4 Interview allows for the determination of neuropathic pain without a clinical examination, having patients be evaluated by a clinician would provide increased validity in outcome ascertainment. We will consider clinical evaluation in the future trial in accordance with the International Association for the Study of Pain's Neuropathic pain Special Interest Group (NeuPSIG) guidelines.[48]

Persistent pain after breast cancer surgery is a common problem and there are no established interventions known to decease its development. The results of this pilot trial are encouraging and provide insights into developing a larger definitive trial.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2019.02.010.

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