ANESTHESIOLOGY

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

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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.

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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

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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

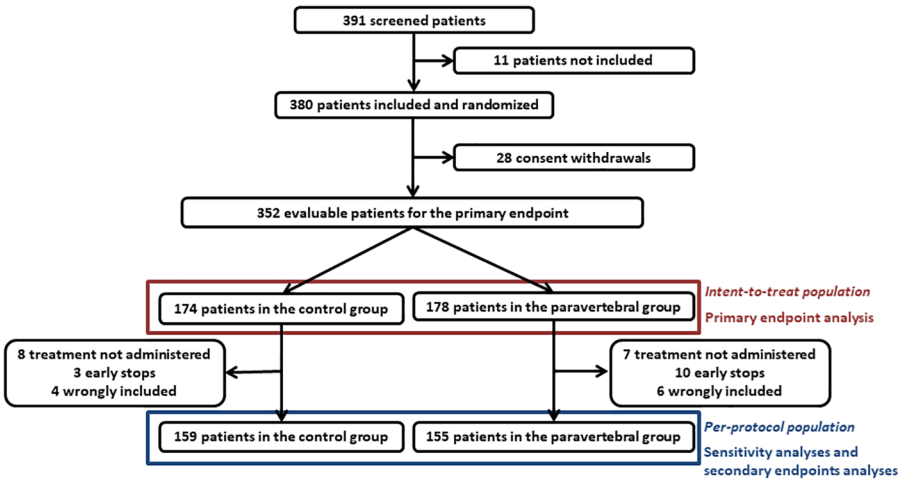

Fig. 1. Flowchart. Control group: thoracic paravertebral block with saline.

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

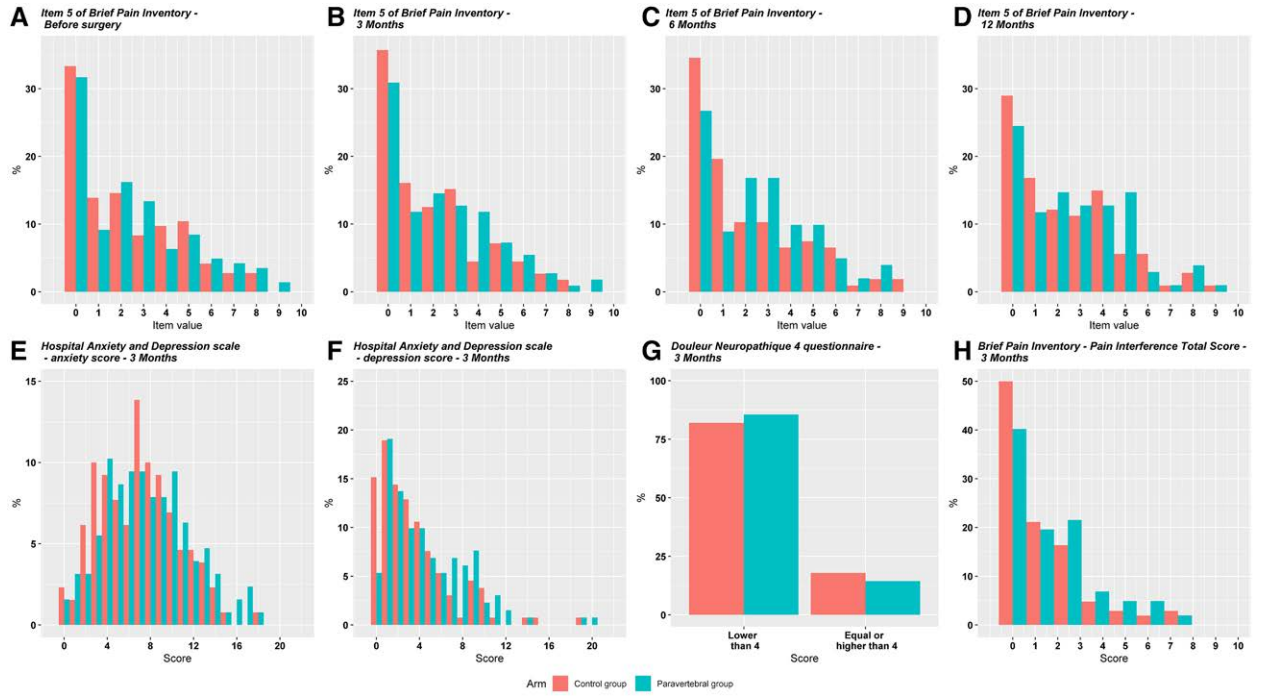

Fig. 2. Brief Pain Inventory before surgery and 3, 6, and 12 months after surgery and Hospital Anxiety and Depression Scale and Douleur Neuropathique 4 questionnaire scores 3 months after surgery. Pain interference at 3 months after surgery was assessed with the Brief Pain Inventory (sleep disturbances, 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

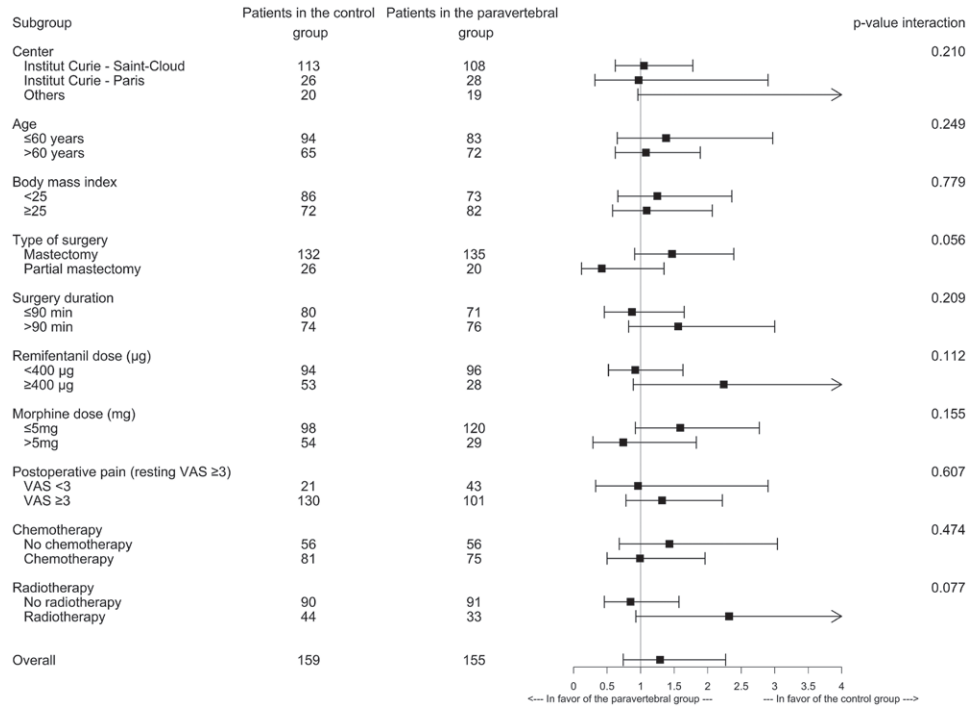

Fig. 3. Forest plot assessing the effects of baseline factors in subgroups groups stratified by treatment (control group or paravertebral group) on chronic postoperative pain 3 months after breast surgery. These results were obtained from the per-protocol population; as for the primary endpoint, the 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

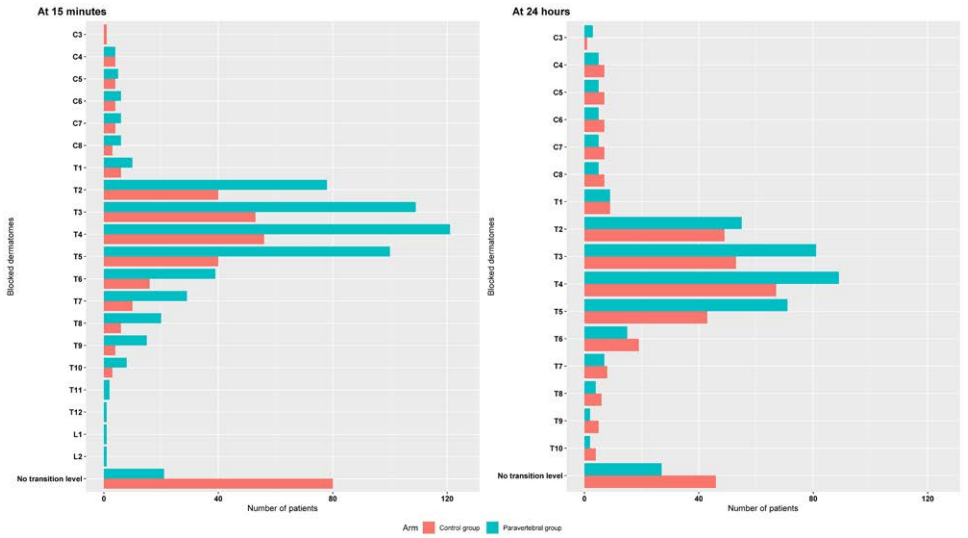

Fig. 4. Blocked dermatomes 15 min and 24 h after an injection of ropivacaine or saline in the paravertebral space in the paravertebral group and control group, respectively. Evaluations of blocked dermatomes were performed through cold ice tests; at 15 min, significantly more patients had at least one 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

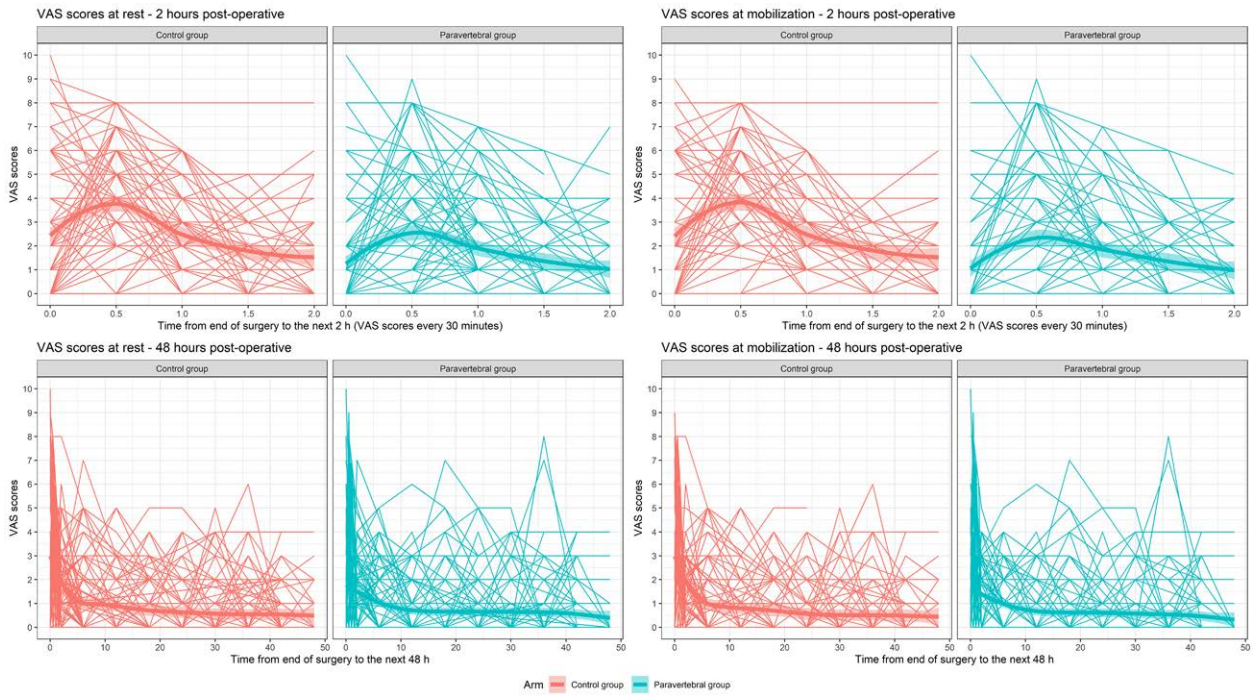

Fig. 5. VAS scores at rest and during mobilization during the first 2 postoperative hours and 48 postoperative hours. In the first 2 postoperative hours, both groups had a maximum pain score approximately 30 min after surgery both at rest and during mobilization. This maximum pain score was higher in 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

Full protocol available at: isabelle.turbiez@curie.fr. Raw data available at: isabelle.turbiez@curie.fr.

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Appendix

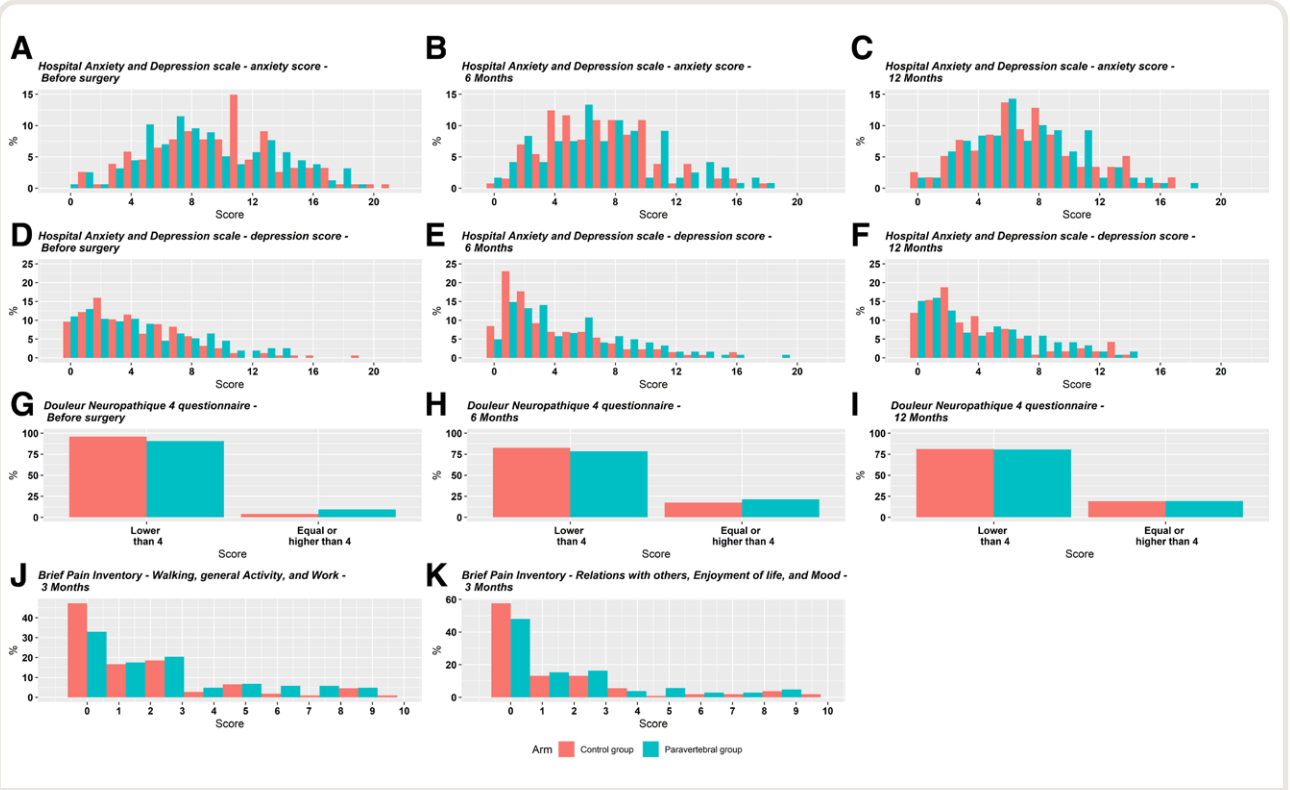

Fig. A1. Secondary endpoints: (*A–C*) Hospital Anxiety Depression Scale-anxiety scores, before surgery and at 6 and 12 months. (*D–F*) Hospital Anxiety Depression Scale-depression scores, before surgery and at 6 and 12 months. (*G–I*) Douleur Neuropathique 4 scores, before surgery and at 6 and 12 months. (*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.