Pain in 1,000 Women Treated for Breast Cancer

A Prospective Study of Pain Sensitivity and Postoperative Pain

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ABSTRACT

Background: This article describes the methods and results of the early part (experimental pain tests and postoperative analgesia) of a study that assesses genetic and other factors related to acute pain and persistent pain after treatment of breast cancer in a prospective cohort of 1,000 women.

Methods: One thousand consenting patients were recruited to the study. Before surgery (breast resection or mastectomy with axillary surgery), the patients filled in questionnaires about health, life style, depression (Beck Depression Inventory), and anxiety (State-Trait Anxiety Inventory). They were also exposed to experimental tests measuring heat (43°C and 48°C, 5 s) and cold (2-4°C) pain intensity and tolerance. Anesthesia was standardized with propofol and remifentanil, and postoperative analgesia was optimized with i.v. oxycodone.

Results: The patients showed significant interindividual variation in heat and cold pain sensitivity and cold pain tolerance. There was a strong correlation between the experimental pain measures across the tests. Presence of chronic pain, the number of previous operations, and particularly state anxiety were related to increased pain sensitivity. Previous smoking correlated with decreased heat pain sensitivity. These factors explained 4–5% of the total variance in pain sensitivity in these tests. Oxycodone consumption during 20 h was significantly higher in patients who had axillary operations

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What We Already Know about This Topic

• Predictors of experimental pain sensitivity and their relationship to acute postoperative pain have been examined in a variety of surgical populations.

What This Article Tells Us That Is New

• In a study of 1,000 women undergoing breast surgery for cancer, a small portion of the variance in preoperative response to noxious heat and cold testing could be explained by anxiety, the presence of chronic pain, and the number of previous operations.

• There was a weak correlation between response to experimental pain testing and acute postoperative pain, with largely similar predictive factors across both 43°C and 48°C tests.

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clearance. Oxycodone consumption had only a weak correlation with the experimental pain measures.  

**Conclusions:** Contact heat and cold pressure tests identify variability in pain sensitivity which is modified by factors such as anxiety, chronic pain, previous surgery, and smoking. High levels of anxiety are connected to increased pain sensitivity in experimental and acute postoperative pain.

**POSTOPERATIVE** pain offers a model to study factors that are related to tissue or nerve injury developing into persistent pain. Since mid 1990s, this has been one of the key research interests in pain. Several studies have indicated that the severity of acute pain is related to persistent postsurgery pain. The intensity of acute pain could reflect the extent of tissue injury. However, a significant body of evidence suggests that there is a great interindividual variation in the perception of standardized acute noxious stimulation indicated by both subjective reports and functional brain imaging. Also, genetic factors have been shown to explain part of the variation in acute pain perception. Thus, a more general increased sensitivity to pain perception could be a common denominator for both acute and chronic pain. In addition to shared genetic factors, mood, cognition, and environmental or lifestyle factors could be related to increased pain sensitivity in general.

In this article, we describe a study where 1,000 women were exposed to experimental contact heat and cold pressure tests before undergoing surgery for breast cancer. Anesthesia and postoperative pain management were standardized and carefully controlled so that the relevant information could be compared with the results from the experimental pain tests. Preoperative data collection included questions about mood and several other factors that could modulate acute pain perception and pain persistence.

The patients of this study will be followed for up to 5 yr to assess what factors are related to persisting pain after treatment of breast cancer. The study also assesses genetics factors using candidate gene approaches and a genome-wide association study.

Previous studies have shown that persistent pain after surgery and adjuvant therapies for breast cancer can have a significant impact on the patient’s quality of life. Chronic posttreatment pain is an unwanted adverse effect in breast cancer survivors who should be able to lead a normal life. The ultimate goal of this project is to identify factors related to susceptibility for more severe acute pain and persistent pain. Preoperative identification of patients at the highest risk would enable targeting preventive studies or interventions, for example, pharmacological or psychological, to those who are most likely to develop persistent pain.

The outcomes of this current report include variation in pain intensity in the thermal heat and cold pressure tests, need of oxycodone during the first 20 postoperative hours, and how these measures are related to each other and to the psychological and lifestyle factors assessed before surgery.

**Materials and Methods**

This prospective study describes a cohort of 1,000 women who were treated for breast cancer and who will be followed for a total of 5 yr after surgery (fig. 1). In this article, we describe the study methodology and results from the experimental pain tests that were performed before surgery and the data related to perioperative analgesia.

**Ethics**

Before enrollment, the entire study was explained to the patients who were fully informed of the study procedures and potential risks. Study subjects were fully apprised of their right to withdraw from the study at any time. Written informed consent was obtained from each subject participating in the study by a research nurse or a physician. Surgery and all other treatments were part of the patients’ normal clinical care under the supervision of the physician in charge.
The research protocol had been approved by the coordinating ethics committee (136/E0/2006) and the ethics committee of the Department of Surgery (Dnro 148/E6/05) of the Hospital District of Helsinki and Uusimaa, Finland.

**Patients**
The data consist of 1,000 patients who had unilateral non-metastasized breast cancer and who underwent surgery for breast cancer at the Breast Surgery Unit, Helsinki University Central Hospital, Helsinki, Finland, between August 2006 and December 2010. Before surgery, the patients participated in a session of two experimental pain tests, such as contact heat and cold pressure.

For this sample, 1,149 patients of the 1,536 eligible consecutive patients were asked to participate in the study. Patients with immediate breast reconstruction were not included. One hundred twenty-six patients (11.0%) declined and 23 patients were withdrawn (in 12 cases due to a contraindication to the anesthetic protocol, in 6 cases because of change in the type of surgery or violation of the protocol, and in 5 cases for logistic reasons).

The women underwent either mastectomy or breast-conserving surgery with sentinel node biopsy, axillary clearance, or both. Surgery was individualized according to the patient and tumor characteristics in agreement with the patient. Surgeries were performed or directly supervised by experienced breast surgeons, and they were carefully recorded.

**Initial Clinical Assessment**
The day before surgery, after informed consent acquisition, medical and medication demographic history was taken (fig. 1). Background data included age, weight and height, number of previous operations (other than breast surgery), previous chronic pain of any kind, preoperative use of hormonal replacement therapy, use of alcohol (no/less than six doses per week/more than six doses per week), alcohol problem in the family (no/yes), and smoking (never/yes/stopped). Pain in the area of the breast/axilla to be operated was assessed in the questionnaire before surgery by a numerical rating scale (NRS 0–10). The patients filled in psychological questionnaires. Sum scores of the Beck Depression Inventory\(^9\) and the Spielberger State-Trait Anxiety Inventory\(^10\) were used. Both inventories have been validated for this particular group of patients, and they have been used in previous studies.\(^2\)\(^,\)\(^11\)

**Experimental Pain**
First, the tests were carefully explained to the patients. Contact heat pain was assessed using the 16 × 16 mm\(^2\) thermode of the TSA-II NeuroSensory Analyzer (Medoc Ltd., Ramat Yishai, Israel). A temperature of 43° and 48°C was exposed, in this order, once each, for 5 s on the volar side of the forearm contralateral to surgery. Patients assessed the intensity and unpleasantness of pain with a 0–10 NRS at the end of the test. Zero represented "no pain" and 10 "worst imaginable pain."

Cold pain was measured by immersing the hand to a cold water (2–4°C) bath (JULABO USA Inc., Allentown, PA) for the maximum time tolerated by the patient but not longer than 90 s. Time to withdrawal as well as intensity and unpleasantness of pain were measured (NRS) at withdrawal and every 15 s during the test. The cold pain test was not performed on the first 100 patients because of unavailability of the device.

**Anesthesia**
The patients were premedicated with diazepam 2.5–15 mg and acetaminophen 1 g orally. In the operation room, i.v. infusion of remifentanil (0.2 µg·kg\(^{-1}\)·min\(^{-1}\)) was started. Anesthesia was induced with propofol (2–3 mg/kg, i.v.). Tracheal intubation was facilitated with rocuronium, and further boluses of rocuronium were administered in order to keep the train-of-four at 0–10% (E-NMT; General Electrics Healthcare Finland, Helsinki, Finland). Mechanical ventilation was adjusted to achieve normocapnia with a 1:1 mixture of oxygen and nitrous oxide. To keep state entropy (the index for monitoring the adequacy of anesthesia; General Electrics Healthcare Finland) at the level of 50 ± 10, a propofol infusion at the rate of 50–100 µg·kg\(^{-1}\)·min\(^{-1}\) was used. Remifentanil infusion (0.05–0.25 µg·kg\(^{-1}\)·min\(^{-1}\)) was adjusted to keep the systolic blood pressure at ±15% of the baseline value minus 20 mmHg. During the closure of skin, fentanyl (1 µg/kg, i.v.), ondansetron (4 mg, i.v.), and dehydrobenzperidol (0.01 mg/kg, i.v.) were given, and the infusion of remifentanil was stopped. At the same time, neostigmine (2.5 mg) with glycopyrrolate (0.5 mg) was given i.v. to reverse the neuromuscular block. Blood specimen was drawn for DNA isolation and banking during anesthesia to avoid unnecessary punctures. Acetaminophen (1 g) was administered orally every 8 h as a basic analgesic according to the local clinical guidelines.

**Postsurgical Pain Assessment and Administration of Oxycodone**
In the post anesthesia care unit, the patients were asked about the pain intensity at rest and during motion. Pain during motion was assessed by asking the patient to raise the arm ipsilateral to surgery up to 90 degree. Patients were titrated with i.v. oxycodone by the research nurse who asked about the pain intensity every 5 min and administered oxycodone in doses of 1–3 mg until adequate analgesia (NRS < 4/10) was achieved. After this, pain intensity was asked every 15 min until the patient needed the next dose of oxycodone. The required quantity of oxycodone was recorded. A blood specimen was drawn for the measurement of the concentrations of oxycodone and its major metabolites when the patients were satisfied for the first time (first state of adequate analgesia) and before the next dose after that was requested. After 2h, the patients were moved to the ward, and they were provided with a patient-controlled analgesia device (Abbott Pain Management ProviderT, Abbott Laboratories, North Chicago, IL, or CADD-LegacyT; Deltec, Inc., St. Paul, MN) for up to 20 h except for 70 day surgery-patients. The total amount of oxycodone consumed

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after the operation (titration at the postanesthesia care unit and patient-controlled analgesia consumption) and any incidents of adverse events were recorded. The postoperative outcome measures studied were: pain intensity during motion at 5 min from waking and when needing the first dose of oxycodone, time to the first dose of oxycodone, time and amount of oxycodone needed to achieve satisfactory pain relief, and oxycodone consumption in the postanesthesia care unit and during 20 h.

**Statistical Analysis**

Data were analyzed using R program package version 2.14.2. Demographic data are summarized as means ± SD or as median (range). The Kruskal–Wallis test was used to determine differences among patient groups divided based on the type of surgery or anxiety status. The effects of age, body mass index (BMI), state anxiety, presence of any preoperative chronic pain condition, pain in the breast/axilla to be operated, and smoking on six experimental pain response and postoperative pain measures (cold pain intensity at 15 s, cold withdrawal time, heat pain intensity at 48°C, postoperative pain intensity during motion when needing the first dose of oxycodone, amount of oxycodone needed to achieve satisfactory pain relief, and oxycodone consumption during 20 h) were evaluated using linear models. For postoperative outcomes, the type of surgery was included in the model as well. An additional model was created for postoperative pain intensity and oxycodone consumption by including experimental pain responses as covariates. Smoking status (nonsmoker, present smoker, previous smoker) was treated as a factor in the linear model. P values were adjusted for the number of tests performed. Because some of the outcomes do not follow normal distribution, the results were rechecked with a permutation testing strategy. Each model was fitted 1,000 times, and the original test statistics was compared with the distribution of the test statistics gained from permutation. The effect of the whole model on the studied variables, that is, the proportion of the total variance explained, is presented using a multiple $r^2$ value. The correlation between different pain measures was determined using Pearson correlation coefficients ($r$).

**Results**

**Patient Characteristics**

Demographic data of the patients, grouped by the type of surgery, and details on anesthesia are shown in table 1. Six hundred twenty-six patients underwent breast-conserving surgery, and of these 206 patients had axillary clearance. Three hundred seventy-four patients underwent mastectomy, and details on anesthesia are shown in table 1. Six hundred twenty-six patients underwent breast-conserving surgery, and of these 234 had also axillary clearance. Patients who needed more extensive surgery reported more preoperative pain in the area to be operated (table 1).

**Pain Intensity Measures in the Experimental Pain Tests**

The great majority of the patients (70%) considered the innocuous 43°C stimulation as nonpainful while a wide range of pain intensities was observed after 48°C stimulation (fig. 2). The mean heat pain intensity score was 0.71 ± 1.39 for the 43°C stimulation compared with 3.51 ± 2.42 at 48°C. There was a positive correlation between the intensity of pain after innocuous (43°C) and noxious (48°C) heat stimulation ($r = 0.57$; table 2).

Of the 900 patients tested, 783 patients (87%) were able to keep their hand in the ice-cold water for at least 15 s. The cold pain intensities at 15 and 30 s are shown in figure 3A. If the patient was no longer able to tolerate the test, she was coded as having the maximum NRS score (10) at that time point. Approximately one fourth of the patients (24%) were able to tolerate the cold water immersion for the maximum of 90 s (fig. 3B). The mean cold pain withdrawal time was 46.4 ± 29.5 s. When the patients were divided into three subgroups based on for how long they tolerated the cold pressure test, ≤45, 46–89, and 90 s, the actual pain intensities were significantly higher in those who tolerated the test for 45 s or less compared with those who tolerated it for the maximum time already at the beginning of the test (fig. 4; $P = 5.1 \times 10^{-45}$ at 15 s). Furthermore, there was a positive correlation between the heat pain intensity after noxious (48°C) stimulation and cold pain intensity (table 2; $r = 0.42$ for cold pain intensity after 15 s of stimulation). Cold withdrawal time and heat pain intensity were also correlated ($r = 0.32$), and figure 5 shows the difference in the heat pain intensity mean values when the patients were divided into three groups by the time they were able to tolerate the cold water.

The sum score of state anxiety had the strongest effect on increased pain sensitivity in both experimental pain tests (table 3). Also, presence of chronic pain of any kind and the number of previous operations increased heat and cold pain intensity scores. Chronic pain also decreased cold withdrawal time (table 3). Previous smoking decreased heat pain sensitivity (table 3) while no statistically significant effect on cold pain was seen. BMI or age had no significant effect on the pain intensities reported by the patients in either the heat pain or cold pressure test. The proportion of the total variance explained by the above-mentioned factors varied from 4 to 5% except for the innocuous (43°C) thermal pain test where only 1.3% of the variance was explained (table 3). The P values produced using the permutation strategy can be found in table 1, Supplemental Digital Content 1, http://links.lww.com/ALN/A1000.

**Acute Postoperative Pain and Oxycodone Consumption**

The postoperative pain phenotypes (time to the first oxycodone dose, pain intensity during motion at 5 min from waking and when needing the first dose of oxycodone, time and amount of oxycodone needed for satisfactory analgesia, and the total oxycodone consumption) after the four different types of surgery are shown in table 1. Patients who underwent axillary clearance needed significantly ($P = 3.6 \times 10^{-7}$) more oxycodone (30 mg/kg) than the patients who did not...
The mean pain intensities during motion and at rest and the proportion of patients needing oxycodone during 90 min after the operation in the four different surgery groups are shown in figure 6.

Different measures of oxycodone consumption were strongly correlated (table 2). Total oxycodone consumption (mg/kg) adjusted by type of surgery showed only a modest correlation with the experimental pain measures ($r = 0.10–0.15$; table 2). Similarly, the correlation between postoperative pain (score during motion at 5 min from waking or when needing the first dose of oxycodone) and experimental pain test scores was weak ($r = 0.07–0.15$).

Among the factors explaining the overall variance in the total oxycodone consumption, the age of the patient ($P < 2 \times 10^{-15}$)
and the type of surgery performed \((P = 0.0006)\) were very significant. The older the patients were the less oxycodone they needed (table 3). Also, several other factors contributed to the explanation of the total variance, for example, higher sum scores of state anxiety were related with significantly higher total oxycodone consumption during 20h \((P = 0.003; \text{table 3})\). Presence of chronic pain of any kind \((P = 0.001)\) and preoperative pain in the breast/axilla to be operated \((P = 0.004)\) also had a positive correlation with oxycodone consumption during 20h. Although oxycodone consumption was corrected for the weight of the patients, the effect of BMI was still evident \((P = 0.0004)\). All these factors together explained approximately 16% of the variance in total oxycodone consumption and more than 9% of the variance in consumption for the first state of pain relief.

Table 2, Supplemental Digital Content 2, http://links.lww.com/ALN/B2, shows the effect of each studied covariate, including the experimental pain tests, on postoperative pain. When the experimental pain variables were included in the model, the proportion of the total variance explained increased by approximately two percentage points.

When the patients were grouped on the basis of their preoperative level of anxiety to low-, moderate-, and high-anxiety groups, the groups differed significantly for almost all of the studied pain variables (table 4). The more anxious the patients were, the higher pain values they reported, the less time they tolerated the cold pressure test, and the more oxycodone they needed for postoperative pain relief.

**Discussion**

Persistent postsurgical pain is a major problem. The prevalence of persistent pain after, for example, surgery for breast cancer varies significantly between studies which have been mainly retrospective or cross-sectional in nature. Several factors have been related to an increased risk for the development of persistent postsurgery pain. The most constantly reported factors include severity of acute postoperative pain and anxiety. Because of the retrospective or cross-sectional nature of the studies, it is not possible to draw any conclusions regarding the causality of these factors.

The current project was designed to study the patients prospectively by assessing the psychological factors and pain sensitivity in general by experimental pain tests before surgery, during surgery, and in the immediate postoperative period. We also asked about several other variables that may sensitize to pain. These included presence of any chronic pain condition, number of previous operations not related to breast cancer, BMI, and smoking. Our study is unique in combining detailed information about the clinical and psychological risk factors, preoperative experimental pain tests, and postoperative pain in a large cohort of 1,000 patients from one center and of an ethnically homogeneous Finnish population.

**Experimental Pain Sensitivity**

Previously, preoperative experimental pain sensitivity measures have been studied expecting that they would predict acute postoperative pain. However, there is only a moderate correlation between an individual’s sensitivity to different types of painful stimuli, and there is no consensus on what pain modalities should be used for clinical prediction purposes. Individual differences in sensitivity to the pain
modalities examined in this study, contact heat and cold pressure pain, have shown to be large.\textsuperscript{5,14} Our results are consistent with these findings, and the range of reported pain intensities after the noxious 48°C stimulus was wide. The cross modality correlation between heat pain intensity after 48°C stimulus and cold pain intensity at 15 s was 0.41 which is within the range of previously reported correlations between contact heat and cold pressure pain of 0.48 in a study of 617 normal subjects and the sex-corrected correlation of 0.32 in a study of 617 normal subjects.

In the cold pressure test, we identified three different groups. The range of reported pain intensities at 15 s was 0.41 which is within the range of previously reported correlations between contact heat and cold pressure pain intensity after 48°C stimulus. One explanation could be that in the more pain-tolerant individuals, the endogenous pain inhibitions were activated.\textsuperscript{15} A similar division of patients according to the pain tolerance has been reported before.\textsuperscript{14,16}

Of the covariates examined in this study, age and BMI showed no effect on experimental pain scores. The mean age of our study patients was 57 yr (range, 28–75). Most previous studies assessing experimental pain sensitivity have included only relatively young patients (18–46 yr).\textsuperscript{5,17} Kim et al.\textsuperscript{18} studied heat pain sensitivity in young (mean age, 27 yr) and old (mean age, 72 yr) subjects. They showed that older patients had decreased heat pain thresholds. Also, BMI (18–51) was not included as a predictor of pain sensitivity. Lautenbacher et al.\textsuperscript{18} studied heat pain sensitivity in young (mean age, 27 yr) and old (mean age, 72 yr) subjects of both sexes. They reported that the heat pain threshold showed no age-related changes. Neziri et al.\textsuperscript{19} established the reference values of mechanical and thermal pain tests in a population of 300 pain-free 20–77-yr-old subjects. They showed that older patients had decreased heat pain thresholds. Also, BMI (18–51) was not related to either heat pain threshold or the withdrawal time in the cold pressure test in accordance with our results. This is of interest because theoretically a larger proportion of subcutaneous fat could have an effect on the cold pain tolerance.

State anxiety was the most significant cofactor in our study and it was related with increased pain sensitivity in all experimental pain tests. Each increase in the State-Trait Anxiety Inventory state sum score with 1 point increased the cold pain scores with 0.03 points and heat pain with 0.02 points and of 90 s, and the intermediate group. In the most sensitive group, the pain intensity ratings were significantly higher already at 15 s and increased steeply. In the two other groups, the pain intensity levels started to plateau after 45 s. One explanation could be that in the more pain-tolerant individuals, the endogenous pain inhibitions were activated.\textsuperscript{15} A similar division of patients according to the pain tolerance has been reported before.\textsuperscript{14,16}
PACU = postanesthesia care unit.

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<th>Time from Waking to Satisfactory Pain Relief (min)</th>
<th>Oxycodone (mg/kg) for Satisfactory Pain Relief</th>
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decreased the cold withdrawal time with 0.44 s. When the patients were divided into three anxiety classes (low, moderate, and high anxiety), the high-anxiety group had significantly higher mean pain scores in each test compared with the low-anxiety group. The effect of anxiety on pain sensitivity has been previously shown in several studies, especially in women.20,21

Chronic pain was related to increased experimental pain sensitivity and need of more oxycodone. Previous studies have indicated chronic pain as a risk factor for more intense acute postoperative pain.22 However, previous chronic pain has not been studied as a factor increasing experimental pain sensitivity before. Also, the number of previous operations has not been reported to increase pain sensitivity before. Altogether, these results indicate that continuous or repeated injury with possible glial activation or other mechanisms of sensitization can be clinically relevant.

Interestingly, preoperative pain in the breast/axilla to be operated had a significant effect on the oxycodone consumption during 20 h while the effect on heat pain sensitivity was small. A recent study showed that preoperative breast pain occurs in over a quarter of patients about to undergo breast cancer surgery and suggested that pro- and anti-inflammatory cytokine genes may have a role in this.23 In our study, a much larger proportion of patients reported some preoperative pain (NRS > 0), but only a few percent of patients reported moderate or severe pain (NRS > 4; table 1).

Previous smoking was related to decreased pain sensitivity in the heat pain test, whereas current smoking had no statistically significant effect on any of the tests. Previous literature has suggested that current smoking would have an analgesic effect.24 Our data do not render support to this. It is unclear why previous smoking would reduce pain sensitivity.

All the above-mentioned cofactors explained approximately 4% of the total interindividual variance in pain sensitivity. This apparently modest proportion of the total variance explained is, however, larger than the 1–1.3% of the variance explained by the sex, as has been reported for heat and cold pain sensitivity.17 However, previous studies have shown that depending on the pain modality, sex is a major source of variation in experimental pain sensitivity explaining up to 15% of the variation.17 The current study had only women which reduces variation significantly. This can be regarded either as a limitation or as a strength, depending on the viewpoint. On the average, women have been shown to have higher pain sensitivity than men.25,26 We did not stratify the women according to their menstrual cycle because no influence of the menstrual phase on the outcome variables of contact heat and cold pressure pain sensitivity has been found.14

### Postoperative Pain and Oxycodone Consumption

In this study, the experimental pain measures showed only a weak correlation with the postoperative pain scores ($r = 0.07–0.15$). The i.v. patient-controlled analgesia consumption of oxycodone was the main surrogate measure of postoperative pain. However, the weight-adjusted and type of surgery–adjusted oxycodone consumption showed only a modest correlation ($r = 0.10–0.15$) with the experimental pain measures. This may be partly due to other factors that correlate with the pharmacokinetics of oxycodone. Older patients consumed less oxycodone which is in line with the previous studies.26 Higher sum scores of state anxiety and presence of any chronic pain showed a significant positive correlation with increased consumption of oxycodone during the 20 postoperative hours. Altogether, type
of surgery, age, BMI, anxiety, and chronic pain explained approximately 16% of the variance in the total oxycodone consumption. Patients reporting high-state anxiety scores should be studied in more detail regarding experimental pain sensitivity, higher need of opioids after surgery, and risk for pain persistence.

Previous studies have reported inconsistent results in the correlations between experimental and postoperative pain intensities. Previous literature suggests that the cold pressure test would change when the factor is present. P values that remain <0.05 after adjusting for the six tests performed are in bold.

BMI = body mass index; SE = standard error.

Table 3. Effects of Each Covariate on the Studied Experimental and Postoperative Pain Phenotypes and the Proportion of the Total Variance Explained by the Whole Model

<table>
<thead>
<tr>
<th>Anxiety Class (Sum Score)</th>
<th>n (Valid)</th>
<th>Cold Pain Intensity, 15 s</th>
<th>Cold Pain Intensity, 30 s</th>
<th>Cold Pain Intensity, Mean</th>
<th>Cold Pain Intensity, Withdrawal</th>
<th>Cold Pain Withdrawal Time</th>
<th>Heat Pain Intensity, 48°C</th>
<th>Pain during Motion 5 min after Waking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (low, 20–39)</td>
<td>536</td>
<td>5.4</td>
<td>7.47</td>
<td>8.04</td>
<td>8.09</td>
<td>48.95</td>
<td>3.31</td>
<td>3.83</td>
</tr>
<tr>
<td>2 (moderate, 40–59)</td>
<td>387</td>
<td>5.88</td>
<td>7.84</td>
<td>8.44</td>
<td>8.51</td>
<td>45.54</td>
<td>3.73</td>
<td>4.28</td>
</tr>
<tr>
<td>3 (high 60–80)</td>
<td>64</td>
<td>7.05</td>
<td>9.09</td>
<td>9.23</td>
<td>8.49</td>
<td>28.95</td>
<td>3.92</td>
<td>3.79</td>
</tr>
<tr>
<td>P value, Kruskal–Wallis test</td>
<td>&lt;1 x 10^-4</td>
<td>&lt;1 x 10^-4</td>
<td>&lt;1 x 10^-4</td>
<td>0.03</td>
<td>&lt;1 x 10^-4</td>
<td>0.008</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

PACU = postanesthesia care unit.

Table 4. Mean Pain Scores and Oxycodone Consumption of the Patients Grouped Based on Their Preoperative Level of Anxiety

<table>
<thead>
<tr>
<th>Anxiety Class (Sum Score)</th>
<th>n</th>
<th>Cold Pain Intensity, 15 s</th>
<th>Cold Pain Intensity, 30 s</th>
<th>Cold Pain Intensity, Mean</th>
<th>Cold Pain Intensity, Withdrawal</th>
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<td>3.79</td>
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<tr>
<td>P value, Kruskal–Wallis test</td>
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<td>&lt;1 x 10^-4</td>
<td>&lt;1 x 10^-4</td>
<td>0.03</td>
<td>&lt;1 x 10^-4</td>
<td>0.008</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

Beta shows the change in the studied variable corresponding to each 1 unit increase in the covariate or in the case of binary covariates change when the factor is present. P values that remain <0.05 after adjusting for the six tests performed are in bold.

BMI = body mass index; SE = standard error.

of surgery, age, BMI, anxiety, and chronic pain explained approximately 16% of the variance in the total oxycodone consumption. Patients reporting high-state anxiety scores should be studied in more detail regarding experimental pain sensitivity, higher need of opioids after surgery, and risk for pain persistence.

Previous studies have reported inconsistent results in the correlations between experimental and postoperative pain intensities. Kim et al. reported no significant correlation between preoperative experimental heat pain sensitivity and either postoperative pain after oral surgery or postoperative analgesic consumption. However, pain after cesarean section has showed either a modest \( r = 0.17 \) or a fairly good correlation of approximately \( r = 0.45 \) with heat pain sensitivity with small sample sizes. Two small studies have reported a significant correlation between preoperative experimental burn injury–related hyperalgesia and postoperative dynamic pain ratings after arthroscopic surgery and between heat hyperalgesia in the knee to be operated and the postoperative i.v. patient-controlled analgesia consumption of morphine after total knee arthroplasty \( r = 0.63 \).

Previous literature suggests that the cold pressure test would be a better predictor of postoperative pain than the simple
Table 4.

<table>
<thead>
<tr>
<th>Anxiety Class</th>
<th>n</th>
<th>Preoperative Level of Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (low, 20–39)</td>
<td>536</td>
<td>5.4</td>
</tr>
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<td>2 (moderate, 40–59)</td>
<td>387</td>
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<td>64</td>
<td>7.05</td>
</tr>
</tbody>
</table>

Table 3.

<table>
<thead>
<tr>
<th>Pain during Motion When the First Dose of Oxycodone Was Needed</th>
<th>Time from Waking to the First Oxycodone Dose (min)</th>
<th>Time from Waking to Satisfactory Pain Relief (min)</th>
<th>Oxycodone (mg) Needed for Satisfactory Pain Relief</th>
<th>Oxycodone (mg/kg) in PACU</th>
<th>Total Oxycodone (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.90</td>
<td>17.1</td>
<td>35.5</td>
<td>8.27</td>
<td>9.21</td>
<td>0.24</td>
</tr>
<tr>
<td>5.13</td>
<td>11.8</td>
<td>37.0</td>
<td>9.10</td>
<td>10.15</td>
<td>0.28</td>
</tr>
<tr>
<td>5.10</td>
<td>11.1</td>
<td>41.7</td>
<td>9.75</td>
<td>10.93</td>
<td>0.33</td>
</tr>
<tr>
<td>0.13</td>
<td>0.0009</td>
<td>0.07</td>
<td>0.01</td>
<td>0.003</td>
<td>&lt;1 × 10⁻⁵</td>
</tr>
</tbody>
</table>

heat pain test. Kim et al.\(^{14}\) showed a significant correlation (r = 0.22) between cold pressure withdrawal time and time to first postoperative analgesic after oral surgery, and Bisgaard et al.\(^{16}\) showed a correlation between cold pressure tolerance and acute pain after laparoscopic cholecystectomy. In the current study, the correlation between cold pressure test measures and postoperative pain and oxycodone consumption was modest. However, it will be interesting to find out whether those patients who tolerated the test for the maximum of 90 s had less persistent pain compared with the other patients. The cold pressure test has been used to study conditioned pain modulation and to correlate it with persistent postsurgery pain.\(^{15}\)

Conclusions

This study confirms the great interindividual variation in the perception of acute experimental thermal stimuli and the need of postoperative opioid. The results render support to the hypothesis that continuous nociceptive stimulation such as chronic pain may sensitize patients to new painful stimuli, both experimental and clinical. Anxiety is closely related to pain perception, and it is one of the most constant factors suggested to increase persistent pain. Patients having high sum scores of state anxiety need special attention in connection to surgery. The cold pressure pain test seems an
interesting tool in the study of individual pain sensitivity as it may be a biomarker of endogenous pain inhibition.

This study was initiated in collaboration with the late K. Steven Lafayette, Ph.D., Consulting Psychologists Press, Inc., 1983

References


Fig. 6. Postoperative pain intensities during a 90-min period in the four different groups of surgery. (A) Shows the pain intensity at rest, (B) the pain intensity during motion, and (C) the proportion of patients who have needed at least one dose of oxycodone. AC = axillary clearance; BCS = breast-conserving surgery; M = mastectomy; NRS = numerical rating scale; SNB = sentinel node biopsy.
Colon-Morales’ Uterine Displacement Device

When a pregnant woman lies flat on her back, the heavy contents of her distended womb can compress one or both of her abdomen’s largest blood vessels (inferior vena cava and/or aorta). Besides alarming symptoms, maternal hypotension and even fetal demise can then occur. To help prevent this “supine hypotensive syndrome,” Dr. Miguel A. Colon-Morales invented a uterine displacement device (above), which can be attached to (or slid under the padding of) the surgical table. To shift the gravid uterus to the patient’s left and avoid compressing central vessels, a 10-inch rod is extended so that its terminal plunger ball is “placed in the space between the last floating rib and the right iliac crest.” On June, 13, 1972, Dr. Colon-Morales was granted U.S. Patent No. 3669118 for his clever “Uterine Displacement Device.” (Copyright © the American Society of Anesthesiologists, Inc.)

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