Video Article

A Quantitative Sensory Testing Paradigm to Obtain Measures of Pain Processing in Patients Undergoing Breast Cancer Surgery

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Abstract

Chronic pain following surgery, persistent postsurgical pain, is an important highly prevalent condition contributing to significant symptom burden and lower quality of life. Persistent postsurgical pain is relatively refractory to treatment hence generating a high need for preventive strategies and treatments. Therefore, the identification of patients at risk of developing persistent pain is an area of active ongoing research. Recently it was demonstrated that peri-operative disruptions in central pain processing may be able to predict persistent postsurgical pain at long term follow-up in breast cancer patients. The aim of the current report is to present a short protocol to obtain pain thresholds to different stimuli at multiple sites and a measure of endogenous analgesia in breast cancer patients. We have used this method successfully in a clinical context and detail some representative results from a clinical study.

Video Link

The video component of this article can be found at https://www.jove.com/video/56918/

Introduction

Chronic pain following surgery, persistent postsurgical pain, is an important condition contributing to significant symptom burden and lower quality of life[1]. Persistent post-surgical pain remains poorly understood, but is broadly recognized as pain lasting more than 3 months after surgery[2]. The condition is common, with estimates of its prevalence ranging from 10% to 50% of all postsurgical patients[3]. High-risk procedures include breast surgery[4], thoracotomy[5], limb amputation[6], and hernia repair[7]. Persistent postsurgical pain is relatively refractory to treatment and thus has generated interest in potential preventive strategies and treatments. A better understanding of predicting and characterizing persistent postoperative pain would help identify the subset of patients who are likely to require additional treatment to optimize their peri-operative pain management.

Recently it was shown that abnormal changes in pain thresholds in response to surgery may be of predictive value for long-term persistent pain development in the context of surgery for breast cancer[8]. Others have stressed the importance of the conditioned pain modulation (CPM) effect in predicting persistent postoperative pain, for example with regards to persistent pain after thoracotomy[5]. CPM is the behavioral correlate of diffuse noxious inhibitory control, a physiological phenomenon where input from peripheral c-fibers results in diffuse inhibition from the brainstem of all incoming stimuli mediated by c-fiber from heterotopic fields[9]. The CPM effect is measured by comparing thresholds to a noxious stimulus, which is measured before and after the application of a second different stimulus, which is referred to as the conditioning stimulus[10].

Current standardized quantitative sensory testing (QST) protocols, such as the German Research Network on Neuropathic Pain protocol[11] are quite extensive and may not be suitable to perform in surgical patients. The aim of the current publication is to detail a short and standardized protocol to obtain both pain thresholds and a CPM effect measurement in breast cancer surgery patients. This protocol is derived from a collaborative protocol between our university and the University of Aalborg, Denmark[12].

Protocol

This protocol has been approved in the context of a previous randomized controlled trial[8] by the human research ethics committee region Arnhem-Nijmegen, the Netherlands (nr. 2004/239).

1. Preparation for Testing

1. **Informed consent:**
    1. Review the informed consent form together with the patient.
    2. Answer any questions that patient may have regarding the study.
    3. Obtain written informed consent by having the patient sign the informed consent form and signing it yourself.

2. **Testing environment:**
    1. Perform all the measurements in the protocol in a stimulus poor and temperature stable environment (~21 °C, no music, no uncovered windows, phones switched off).
    NOTE: The clothing of the experimenter needs to be as neutral as possible, i.e. wear a lab coat, be 'naked below the elbows,' wear no jewelry, and wear no perfume. It is well known that experimenter related factors may have influence on the outcome of the measurements. Some of these factors are not completely standardizable (*e.g.* sex), but one should keep this in mind when preparing the performance of the measurements.
    2. During measurements, ensure that the patient and the researcher are the only people in the room, ask others to leave.
    3. Attach a 'do not disturb' sign to the door to avoid being disturbed during the measurements.
    4. Perform all testing with the patient in the supine position on the bed, except for the CPM test, which is performed with the patient in sitting position.

3. **Sites of testing:**
    1. Mark the following sites for threshold testing using a surgical skin marker:
    area under the greater tubercle on bilateral shoulders (C5 dermatome, pressure and electric thresholds), the bilateral thenar (C6, dermatome, pressure), on bilateral iliac crests (L1 dermatome, pressure and electric), bilateral in the mid axillary line at nipple height or 7 cm from the surgical incision in case of breast cancer surgery (T4 dermatome, pressure and electric thresholds).
    2. Mark the CPM testing site using a surgical skin marker: 15 cm above the patella on the non-dominant body site (L3 dermatome, pressure).
    3. Mark a test run site using a surgical skin marker, for example, 15 cm above the patella on the dominant body site.

4. **Electrical stimulation configuration:**
    1. Apply two self-adhesive skin electrodes on each side of the marked spot on each electrical stimulation test site. Place the electrodes with their outer diameter such that they are just touching each other at the marked spot.
    2. Set the QST stimulator to deliver tetanic stimulation (100 Hz, 0.2 ms square waves) – **Figure 1**. Set the ramping rate to 1 mA/s. Set the initial current to 0 mA, the maximum current is automatically set to 50 mA for safety purposes.

2. Electrical Pain Thresholds

1. **Delivery of electricity:**
    1. Use the QST stimulator. Connect the self-adhesive electrodes to the stimulator using the connection leads.

2. **Measurement of visual analogue scale (VAS):**
    1. Use the VAS slider connected to the QST stimulator to obtain VAS scores. The VAS slider consists of a box with a mobile lever on a horizontal bar that represents the VAS. Hand the slider to the patient.
    2. Explain to the patient how to use the slider: *"The control unit has a slider. This slider can be moved to indicate how you experience the stimulus on a scale of no pain to the worst imaginable pain."*

3. Test run:
    1. Explain the procedure for the electrical detection threshold (EDT) to the patient: "*We will conduct a test run to get you familiarized with the measurement. The stimulation will start when you press the button, will gradually increase, and will stop immediately upon letting go of the button. Please press the button when I tell you to do so and let go when you feel anything."*
    NOTE: All instructions are read from a manual to aid in standardization.
    2. Perform a single test run on the test run site to demonstrate the procedure. Record the result on the measurement sheet — **Figure 2**. Make sure the patient cannot read the values of the measurements during the execution of the tests.
    3. Ask the patient to indicate how he/she experienced the stimulus using the VAS slider and note the result.
    4. Explain the procedure for the electrical pain threshold (EPT) to the patient: *"We will conduct a test run to get you familiarized with the measurement. This test is aimed at determining your pain perception in response to electrical stimulation. The stimulation will start when you press the button, will gradually increase, and will stop immediately upon letting go of the button. Please press the button when I tell you to do so and let go when the stimulation becomes painful."*
    5. Perform a single test run on the testing site to demonstrate the procedure. Record the result on the measurement sheet.
    6. Ask the patient to indicate how he/she experienced the stimulus using the VAS slider and note the result.

4. **Measurement:**
    1. Explain the procedure for EDT again to the patient, using wording from 2.3.1.
    2. Measure the EDT at the different study sites (first C5, then T4, then L1). Perform EDT measurement three times at each measurement site, allow at least 15 seconds in between measurements to avoid windup effects.
    3. Ask the patient to rate the associated pain on VAS after the last EDT measurement at each site. Note electrical values and VAS scores on the measurement sheet. Make sure the patient cannot read the values of the measurements during the execution of the tests.
    4. Explain the procedure to determine the EPT again using wording from 2.3.4.

5. Measure the EPT at the different study sites (first C5, then T4, then L1). Perform EPT measurement three times at each measurement site, allow at least 15 seconds in between measurements to avoid windup effects.
6. Ask the patient to rate the associated pain on VAS after the last EPT measurement at each site.
7. Note test electrical values and VAS scores on the measurement sheet. Make sure the patient cannot read the values of the measurements during the execution of the tests.

3. Pressure Pain Thresholds

1. **Delivery of pressure:**
    1. Deliver pressure with the pressure algometer with a 1.0 cm^2 probe under a 90° angle. Use a ramping rate of ~5 N/s by manually adjusting the applied pressure and the pressure on the display. Start at 0 N and apply up to a maximum of 200 N for safety purposes. NOTE: Be careful not to let the device skid on the skin. To prevent skidding of the algometer it is important to place the probe perpendicular to the skin and to support the algometer with both hands while slowly increasing the pressure. The researcher should stand firmly to provide a controlled increase in pressure.

2. **Test run:**
    1. Explain the procedure to the patient: *"We will conduct a test run to get you familiarized with the measurement. This measurement is aimed at determining your perception of pressure pain in muscle. I will put a pressure measurement device on your muscle and will gradually increase the pressure. Please notify me when the pressure feeling becomes throbbing, burning, or painful by saying 'now.'"*
    2. Perform a single test run on the test site. Make sure the patient cannot read the values of the measurements during the execution of the tests. Record the result on the measurement sheet.

3. **Measurement:**
    1. Repeat the instructions for patient using wording from 3.2.1.
    2. Apply pressure to the different study sites (first C5, then C6, then T4, then L1). Perform pressure pain threshold (PPT) measurement two times at each measurement site, allow at least 15 seconds in between measurements to avoid windup effects.
    3. Ask the patient to rate the associated pain on VAS after the last PPT measurement at each site.
    4. Note test pressure values and VAS scores on the measurement sheet.

4. Conditioned Pain Modulation Paradigm

1. **Preconditioning test stimulus**
    1. Repeat 3.1.1. but use PPT as test stimulus. Repeat the instructions for patient using wording from 3.2.1.
    2. Measure pre-conditioning PPT at the CPM testing site (*m. rectus femoris* (L3) on the non-dominant side, 15 cm above the patella). Ask the patient to rate the associated pain on the VAS slider. Note the value at which the pressure become painful and the associated pain score.
    3. Explain the ice water procedure to the patient: *"This is a test to gain information on the way your body processes different pain signals at the same time. I will ask you to submerse your hand into the ice water in the bucket. Place your hand in the water until the wrist and with the fingers spread. Please hold your hand in the ice water until you can no longer tolerate it."*
    4. Tell the patient to remove their hand from the water after 3 minutes of immersion or sooner if the pain becomes intolerable. *"Every 10 seconds, I will ask you to rate the pain on a 0 to 10 scale, in which 0 represents no pain and 10 unbearable pain. After you take your hand out of the ice water we will measure the pressure pain threshold on your leg again, similar to how we did that before."*

2. **Conditioning stimulus:**
    1. Use the cold pressor task as conditioning stimulus. Measure the water temperature using a temperature probe and note the temperature (target temperature between 1 °C and 4 °C).
    2. Ask patient to immerse dominant hand in ice-chilled water. Ask the patient to rate the pain throughout the cold pressure task every 10 seconds on VAS and note the result. Note the completed immersion time on the measurement sheet (maximum duration is 180 seconds, on average 56 ± 55 s[8]).

3. **Determine test stimulus post-conditioning:**
    1. Measure PPT on the CPM test site after the conditioning stimulus. Ask the patient to rate the associated pain on VAS and note PPT and VAS score on sheet.

5. Calculations

1. **EPTs:**
    1. Calculate the mean value for each testing location of the EDTs and EPTs.

2. **PPTs:**
    1. Calculate the mean value for each testing location of the PPTs.

3. **CPM:**
    1. Determine the CPM effect by calculating the relative change (in %) in the PPT at the CPM test location before and after the conditioning stimulus[10].

$$CPM = ([PPT_{post} – PPT_{pre}] / PPT_{pre}) * 100$$

CPM = conditioned pain modulation; PPT = pressure pain threshold.

Representative Results

In a previously published clinical trial in women (*N* = 94) undergoing surgery for breast cancer, we measured electrical and pressure pain thresholds as well as CPM using the protocol described in this report[8]. We performed the testing paradigm pre-operatively and at various time points throughout the year following surgery. We found that women who developed persistent postsurgical pain 12 months after breast cancer surgery, defined as a VAS of >30 mm, exhibit lower pressure pain thresholds both early and late after surgery. **Figure 3** details the changes in pressure pain thresholds both early (**Figure 3A**) and late (**Figure 3B**) after surgery. For simplicity's sake, the pressure pain thresholds at different measurement sites are summated and expressed as change vs. baseline. Using logistic regression, we found that for every 10% lower thresholds 5 days after surgery, patients were 50% more likely to exhibit chronic pain at 12 months after surgery (confidence interval 10–100% more likely, $p = 0.01$).

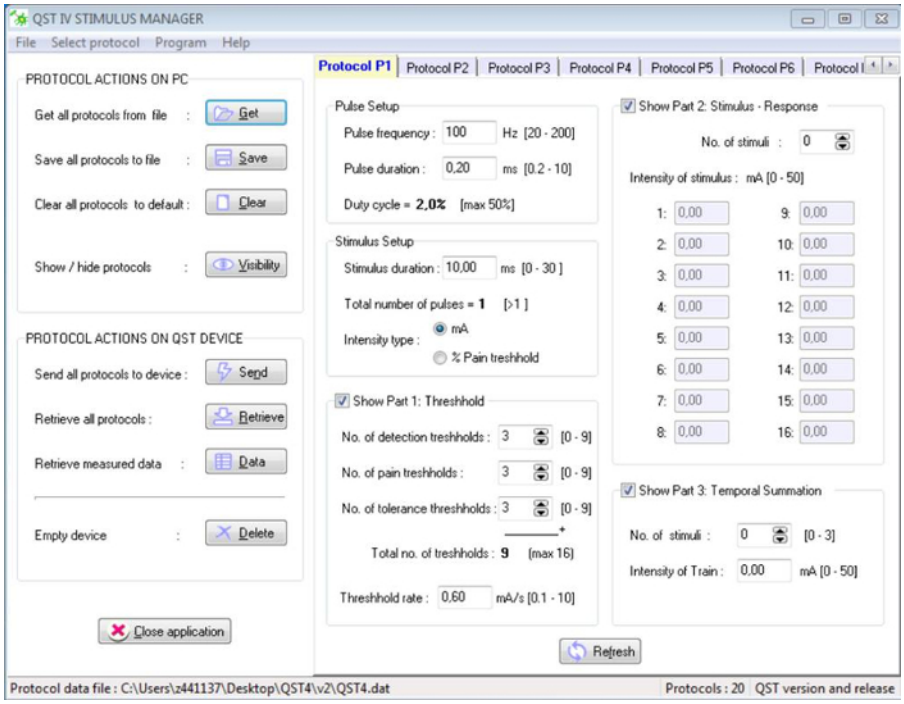

Figure 1: Screenshot of the software interface and the appropriate settings to be used for electrical QST measurement. Please click here to view a larger version of this figure.

Name researcher: _____ Date: _____Humidity:_____

Study ID: _____ Measurement #: _____Temparature:_____

O Left handed **O** Right handed **O** Left side surgery **O** Right sight surgery

Time: _____ Remarks:_____

Electrical thresholds (EDT, EPT)										
		EDT 1	EDT 2	EDT 3	VAS		EPT 1	EPT 2	EPT 3	VAS
Test		mA	mA	mA	VAS		mA	mA	mA	VAS
C5	Left	mA	mA	mA	VAS		mA	mA	mA	VAS
	Right	mA	mA	mA	VAS		mA	mA	mA	VAS
T4	Left	mA	mA	mA	VAS		mA	mA	mA	VAS
	Right	mA	mA	mA	VAS		mA	mA	mA	VAS
L1	Left	mA	mA	mA	VAS		mA	mA	mA	VAS
	Right	mA	mA	mA	VAS		mA	mA	mA	VAS

Pressure algometry (PA)					
		PPT 1	PPT 2	PPT 1	PPT 2
Test		N	VAS	N	VAS
C5	Left	N	VAS	N	VAS
	Right	N	VAS	N	VAS
C6	Left	N	VAS	N	VAS
	Right	N	VAS	N	VAS
T4	Left	N	VAS	N	VAS
	Right	N	VAS	N	VAS
L1	Left	N	VAS	N	VAS
	Right	N	VAS	N	VAS

Conditioned Pain Modulation (CPM)										
	PA		**O** Left hand submerged **O** Right hand submerged							
L3	N	VAS								
IWB 0	10	20	30	40	50	60	70	80	90	
	100	110	120	130	140	150	160	170	180	
	PA									
L3	N	VAS	Water temperature:_____							

Figure 2: Scoring sheet. N: Newton; mA: milliAmpere; VAS: visual analogue scale; EDT: Electrical detection threshold; EPT: Electrical pain threshold; CPM, Conditioned pain modulation; PA: Pressure algometry; IWB: Ice water bucket test. Please click here to view a larger version of this figure.

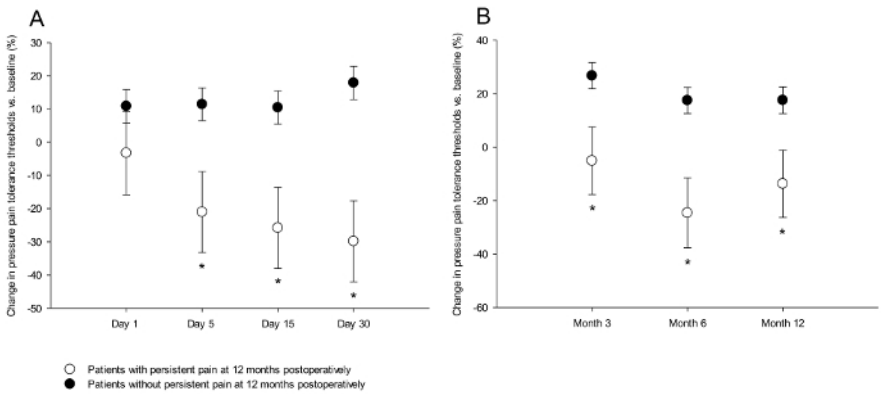

Figure 3: Change in pressure pain thresholds in the year following breast cancer surgery. Panels **A** and **B** show the mean ± SE at the early and late postoperative time points, respectively. Time points are labeled in relationship to surgery, baseline assessment was ~1 week prior to surgery. Analysis was by mixed models analysis using factors 'Time' and 'Persistent Pain' with Bonferroni corrected *post hoc* comparison of individual time points. *Different vs. patients without persistent pain at 12 months postoperatively (α-level 0.05), specifically: $p = 0.02$ at day 5; $p < 0.01$ at day 15; $p < 0.01$ at 30 days; $p = 0.02$ at 3 months; $p \leq 0.01$ at 6 months and; $p = 0.03$ at 12 months. This figure has been modified from van Helmond *et al.*[8]. Please click here to view a larger version of this figure.

Discussion

Our method of quantifying pressure pain thresholds, electrical pain thresholds, and CPM can be successfully applied in a clinical context given its short duration (~20 minutes). We have previously shown that pressure pain values obtained early after surgery may be of value in predicting persistent pain at long term follow-up in the context of breast cancer surgery[8]. While electrical pain thresholds CPM were not predictive of persistent pain in our study, others have shown that these measures may be of value with regards to other procedures[5,13]. A limitation of using electrical pain thresholds is that it may represent an unnatural stimulus. However, the fact that it bypasses local modulation and that it offers very precise control over intensity and timing, improving repeatability, led us to include it in the current protocol[14]. Alternative stimulus modalities, such as heat, could potentially be used to replace the electrical stimulus in the present protocol.

We hope that detailing a circumscribed, yet valuable, quantitative sensory testing paradigm will lead to wider application of these measures in the context of the study of persistent pain after breast cancer. Once more perioperative quantitative sensory testing data become available it may be possible to identify subpopulations of patients that are at high risk of developing persistent postsurgical pain, and to tailor periprocedural treatments to minimize the risk of eventually developing persistent pain.

Disclosures

The authors have no conflicts of interests or any financial interests to disclose.

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