EEG as a predictor for acute postoperative pain and the development of chronic postsurgical pain after breast cancer surgery

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Primary Objective: 1. A search for (objective) EEG predictors (independent variables) for both acute and chronic postoperative pain (dependent variables) after breast cancer surgery. The EEG variables are derived from the above mentioned five...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON36597

Source
ToetsingOnline

Brief title
EEG and pain after breast cancer surgery

Condition

- Other condition
- Breast neoplasms malignant and unspecified (incl nipple)
- Breast therapeutic procedures

Synonym
postoperative pain (acute&chronic) after breast cancer surgery

Health condition

postoperatieve pijn (acuut en chronisch) na borstkanker chirurgie

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: breast cancer, chronic pain, EEG, postoperative pain

Outcome measures

Primary outcome

Primary study parameters/endpoint

1. EEG parameters

Firstly, we will try to demonstrate a (predictive) relationship between baseline EEG measures (obtained before the five experimental tasks) and acute postoperative pain and CPSP (as measured at six months follow-up).
Secondly, similar predictive relationships are to be determined between EEG/ERP outcome parameters of the five *vulnerability* experiments and acute postoperative pain and CPSP.

2. Pain Intensity

During the acute postoperative phase is measured by NRS scales assessing average pain, pain in rest and during movement, and pain at that very moment at a fixed time each day, starting at the day of the operation until 7 days after the operation. Also the DN4 questionnaire is used, a short instrument to assess the neuropathic aspects of pain39.

3. Pain intensity at 3, 6 and 12 months postoperatively: This is assessed by the Brief pain inventory-short form (BPI-SF). It is a 12 item questionnaire which measures pain during the past 24 hours. The BPI-SF has two subscales: pain severity and pain interference. The questionnaire is validated for the Dutch language and is widely used for postoperative pain and pain in cancer patients40. The scale is slightly adapted to specifically refer to pain associated with the surgical procedure. This adaptation is adopted from the study, being conducted by Prof M. Peters, called *Recovery after hysterectomy: A multicentre study into influencing factors which has started recently in our hospital. In our questionnaire we specifically ask for pain in the region of the breast in the postoperative period. The neuropathic character of pain is measured with the DN4.

Secondary outcome

Physical functioning will be measured with the physical functioning subscale of the SF36. This subscale consists of 10 items assessing perceived difficulties in physical activities (walking, climbing stairs. etc.).

Self-perceived recovery is assessed with the Global Surgical Recovery Scale (GSR). The GSR consist of one item on which patients score how much they feel themselves recovered (0 - 100%). This scale is used previously as an outcome measure in a surgical cohort study in our hospital.

Study description

Background summary

A worldwide clinical observation is that a certain number of patients who have undergone surgery suffer from acute postoperative pain. Despite interventions such as implementation of acute pain services and specific pain management procedures, a significant number of patients experience acute postoperative pain and develop chronic postsurgical pain (CPSP). CPSP is characterized as continuous or recurrent pain, persisting beyond normal healing time. The term *chronic* refers to a period exceeding three months. Several studies reported negative consequences of postoperative pain and CPSP, ranging from immediate internal physiological problems (cardiac, pulmonal and gastrointestinal), prolonged recovery time, psychological complaints such as depression, anxiety and a decreased quality of life, as well as socio-economic problems (resumption of work and extra use of the health care system).
There is consensus that chronic pain states are multidimensional in nature. A large body of literature exists, illustrating the effects of somatic, psychological and socio-cultural factors in both the development and maintenance of chronic pain. How these multidimensional factors are interrelated is still the topic of much debate and research.
Especially patients undergoing breast surgery are at risk of developing CPSP. Estimates of the prevalence of chronic pain after breast surgery have been presented in a recent study in Denmark. Of 1543 patients 13% perceived severe pain and 39% reported moderate pain. In another study of 196 patients, 20% had severe pain in the first month after a partial or complete mastectomy. Besides the damage of the operation and therefore the level of acute pain, at least three (psychological) factors may play a role in the chronification process: First, being aware of the probability of having a life-threatening disease is emotionally severely distressing. Second, as was shown recently, response expectancies, coping strategies, optimism (catastrophizing thoughts about post-surgical complaints and outcome) are likely to contribute to patients* experiences of complaints after breast surgery. Third, the physical integrity of the feminine body, by lumpectomy or mastectomy, is damaged, having several possible consequences at the psychological level (depression, disturbed body image, sexual / relational problems, etc).
In attempts to predict CPSP, at least four categories of variables have been investigated: patient characteristics, preoperative psychological variables, operation-related variables and genetic factors (see figure 1), with suggestions of increased risk related to factors from all categories.
In order to measure psychological variables, studies almost without exception rely on self-report questionnaires. It is known, however, that data derived from such questionnaires are subject to several forms of bias. As a result, a trend in recent studies is to validate questionnaire-based data with objective psychophysiological measures. An example is the work by Vossen et al. who tried to demonstrate how subjectively reported pain is associated with specific EEG parameters, namely the N2 and P3 components of the pain event-related potential (ERP). The authors concluded that ERP was associated with self-reported pain in

daily life up to two weeks later. Furthermore, it was demonstrated that depressed patients with chronic back pain showed less habituation to experimental pain stimuli. Another study by Nir et al utilized continuous EEG to investigate the properties of peak alpha frequency (PAF) as an objective cortical measure associated with subjective perception of tonic pain. Additionally, a study investigated the mechanism of attentional effect of pain. Pain was closely associated with changes in neuronal gamma oscillations in the human brain. The authors stated that in the hypervigilant state of chronic pain, maladaptive changes in the attentional effects of pain may be associated with abnormal changes in neuronal gamma oscillations. This may represent a possible mechanism in the pathophysiology of chronic pain.
In sum, it is known that several pre- and perioperative factors play a predictive role in the severity of acute postoperative pain and the development of CPSP. Additionally, EEG measurements associated with pain are emerging, but prediction of clinical pain with EEG has not been studied yet. Furthermore, in the field of chronic pain, the onset of psychophysiological mechanisms remains to be elucidated. Thus EEG measures may be informative in this regard, and may give us a more objective measure of pain.

This study focuses on predictability of acute postoperative pain as well as CPSP based on the results of five so called psychophysiological *vulnerability* experiments.
1. Experiments investigating attentional bias towards pain. In a recent review, the significance of attentional bias towards pain as a risk factor in the chronification process of pain was demonstrated. Therefore, the hypothesis that in a population of breast cancer patients attentional bias towards pain-related words is associated with cortical activity, as measured with EEG / ERP, requires further examination.
2. A large body of literature exists, showing an association between abnormal stress reactivity (measured as muscle-reactivity and heart rate) and the development of chronic pain. Rehabilitation centre *t Roessingh in Enschede in the Netherlands has substantial experience in performing such experiments, and many articles supervised by Prof. Hermens have been published.
3. As already mentioned above, a dissertation project carried out at Maastricht University demonstrated the importance of abnormal habituation as a possible mechanism in the chronification process of pain.
4. Mood reactivity can be experimentally manipulated by so called *mood inductions*. Examples are: looking at pictures or movies with different emotional content. Especially in research concerning depression, the degree of reactivity seems to be a significant *vulnerability* parameter. Because of the strong relationship between chronic pain and depression, abnormal mood reactivity might also be an important factor in the chronification of postoperative pain.
5. Recently, a brief task was developed assessing variation in detecting affectively meaningful speech (speech illusion) in neutral random signals (white noise) and the

degree to which this was associated with psychological instability, which is also predicted to contribute to development of pain as an underlying marker of affective dysregulation, a phenomenon which is likely to occur in varying degrees after breast surgery.

Apart from a preoperative baseline-EEG and the five vulnerability experiments, a second follow-up EEG is required in order to yield insight into cortical responsiveness to the five vulnerability experiments changes over time, and how this is associated with changes in pain perception. Stated in another way: a follow-up EEG enables us to investigate changes in the EEG between patients with or without CPSP, and changes therein.
More insight into the five psychophysiological vulnerability mechanisms may help in the process of identifying patients *at risk* (based on a preoperative assessment EEG-protocol), for developing acute postoperative pain and CPSP. Secondly, the protocol may be used as a tool to evaluate the effect of future (preventive) interventions. Finally, the results may lead to the development of new *tailor-made* treatments.
The choice of patients undergoing breast cancer surgery is deliberate: First, the vast majority of these patients do not experience pain in the region of the breast preoperatively. This is in contrast to most other populations undergoing an operation. Second, it is known that crucial psychological factors such as depression and anxiety (which influence the development of chronic pain) are prominent. The occurrence of depression and anxiety in breast cancer patients lies between 25-35%. Third, the observed prevalence of CPSP in this group is relatively high, at 20-52%.

Study objective

Primary Objective:
1. A search for (objective) EEG predictors (independent variables) for both acute and chronic postoperative pain (dependent variables) after breast cancer surgery. The EEG variables are derived from the above mentioned five vulnerability experiments.

Secondary Objectives:
1. To determine if, in response to the five vulnerability experiments, there are changes in cortical processing in relation to the chronification process of postoperative pain.
2. To compare the EEG/ERP t0 and t6 months results in the breast surgery population with a general (non-surgical, female) population with respect to the development of chronic pain.
3. Determination of the prevalence of CPSP after mamma surgery in MUMC.
4. To compare the influence of psychosocial factors, measured with questionnaires between breast cancer patients and patients undergoing a hysterectomy with no underlying cancer (see the Peeters, Theunissen, Marcus et al study currently being performed in the MUMC).

Study design

A prospective cohort study with five moments of assessment:

a. preoperative
b. perioperative up to day 4 postoperatively
c. follow-up 1 (at 3 months)
d. follow-up 2 (at 6 months)
e. follow-up 3 (at 12 months)

Preoperatively and at 6 months, the assessments consist of an psychophysiological (EEG, ECG, EMG) registration while performing the five vulnerability tasks, as well as several health-related and psychological questionnaires.
Perioperative data concerning type of surgery, amount of analgesia, and subjective pain ratings are collected. In the first four days after surgery patients are asked to complete a pain diary. At follow-up 1 and 3 a questionnaire measuring the presence of CPSP and health status is mailed.

Study burden and risks

There is no benefit for patients participating in the study. No financial (or other) reward will be given. Travel expenses will be compensated. There are no risks involved. We estimate the burden for the patient to be moderate because of the following two factors:
1. A twofold EEG measurement (of two and a half hours each), which takes place at the university, outside the hospital.
2. The completion of several pain- and health related questionnaires, which is approximately 1 hour before the operation and 30 minutes at three months, six months and at one year follow-up

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Age 18 - 65 years.
• ASA 1-2.
• Sufficient comprehension of the Dutch spoken and written language.
• Elective curative breast cancer surgery, both mastectomy and breast-conserving surgery
• Stage I and II breast cancer.

Exclusion criteria

• Previous breast surgery, both ipsilateral and contralateral.
• Stage III-IV breast cancer.
• Chronic pain (>3months) with an average severity of at least a VAS score of 4 during the last two weeks.
• Chronic pain for which invasive treatment is needed.
• Use of (weak / strong) opioids in the last week.
• A history of opioid addiction.
• Regular use of the following medications in the last year: antiepileptics, antipsychotics and anxiolytics.
• ASA 3 or higher.
• Consumption of alcohol (>4 units) and / or drugs the evening before.
• Alcohol consumption (>= 5 units/day).
• Illiteracy, problems with self expression, language barrier.
• Serious visus and / or hearing problems, interfering the performance of the experimental tasks.
• A history of psychiatric complaints and/or epilepsy .

• A medical history of CVA or TIA.
• Previous breast surgery.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-08-2011
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO

Date:	02-05-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL34275.068.11