euCPSP: European observational study on chronic post surgical pain
(PAIN OUT Study)
Sponsor: European Society of Anaesthesiology
Collaborator: University of Jena, Germany
ClinicalTrials.gov Identifier: NCT01467102
Study Protocol Amendment 1
Version 2.0
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euCPSP-PAIN OUT Study Protocol Amendment 1, version 2.0. 28 March 2012
**Introduction**

Over the past ten years it is well recognized that chronic post-surgical pain (CPSP) is a significant medical problem. CPSP has an estimated mean incidence of 30% with variation depending on the type of surgery. The incidence of severe CPSP with significant functional impairment is estimated to be 5-10% and effective approaches to prevent CPSP are basically unknown. Every year, surgery is performed on over 40 million patients in the European Union, therefore the number of patients potentially exposed to CPSP is large and CPSP may represent a major, largely unresolved clinical problem. Most studies on CPSP have collected data in a single institution or at a national level. No data have been collected at an international level on very large samples of patients by using the same methodology. Most studies with patient-based data in the surgical period investigated one specific type of surgery and included a limited number of patients. On the other hand, the largest nationwide studies following large sample of patients collected retrospective data for the postoperative period with limited validity. Since the generalization of these results is not feasible, we need large prospective studies on incidence and risk factors of CPSP.

PAIN OUT is a research group already working at a European level on quality improvement of acute postoperative pain management with a collaboration of clinicians, researchers and software engineers. Collaboration between PAIN OUT network and ESA Clinical Trials Network (CTN) would provide an opportunity to create a large prospective study not only on acute pain but also on CPSP.

The main goal of our proposal is to obtain a generalizable epidemiology of CPSP by performing a large data collection in many European countries. The large sample will allow analysis of the incidence of CPSP, differences in incidence patterns in Europe, incidence in rare types of surgeries and specific populations. This observational, prospective study will help to better anticipate and potentially prevent the development of CPSP. In fact when CPSP occurs patients are frequently undiagnosed and pain is poorly managed such that patients may develop refractory chronic pain. Surgery is a major cause of chronic pain and it is unique in that there is potential to prevent it from occurring. Data from this study might alert respectively surgeons and anaesthetists about the most important types of surgery and some perioperative techniques of pain prevention with an impact on the incidence of CPSP.
Anaesthesiologists, who are leading this project, might therefore, have an important role in preventing future cases of CPSP.

Research questions
1. What is the incidence of CPSP in Europe?
2. What are the risk factors of CPSP related to surgery, patient and anaesthesia management?
3. What are the difference in incidence and risk factors in different European countries?

Study design
This project is a European observational study on the incidence and characteristics of CPSP.

Inclusion / exclusion criteria
- Patient 18 years old and above
- Patient has given consent; patient is able to fill in questionnaire on his/her own, unaided (exceptions are patients who are unable to fill in the questionnaire for technical reasons, e.g. cannot write due to the surgery (e.g. their arm in a cast) or unable to see the text (e.g. spectacles not available); patient is in department, available for interview.
- Patient is capable of participating in the CPSP incidence study (i.e. capable to fill the questionnaires on the website at 6 and 12 months after surgery).
- Time of data collection immediately after surgery is POD1 and 24±12 hours after surgery.
- Patient has not undergone repeat surgery (same organ) during current hospitalization.
- Patient has undergone a surgery include in the list (see Appendix 1)

Participating centres
We expect that at least 30 ESA CTN sites from Europe will be able to participate and recruit for one and a half year.
**Ethical considerations**
Approval for the study will be obtained from the local ethics committee of each site which participates in the project.

**Data collection**
Patients scheduled for a specified list of surgeries will be included (Appendix 1). Data will be collected prospectively by investigators at day 1 after surgery using a standardized questionnaire validated by the PAIN OUT network. Data collected include: patient demographics, short medical history, and type of surgery using a validated classification code (ICD-9; http://www.code-xpert.com/indexx.html), data on anaesthesia, analgesia and patient-reported outcomes (Appendix 2). Patients fill in the Outcomes questionnaire and the investigator the rest of the data items based on the medical record.
All patients will be asked to fill the Brief Pain Inventory (BPI) and the DN4 questionnaires, at 6 and 12 months after surgery (Appendix 3). They will do it directly on a dedicated website. The main outcome measure will be the incidence of CPSP 12 months after surgery. Secondary outcome measures will be CPSP 6 months after surgery, risk factors of CPSP related to the patient, surgery, anaesthesia and analgesia.
If the patient has no personal e-mail address it will be possible to propose a follow up by phone call at 6 and 12 months.

**Data set**
Participating centres will become members of PAIN OUT International. This entails the right to use the questionnaires developed by PAIN OUT for collecting data about post-operative pain in the first day after surgery, training about the methodology of data collection and web-based input, access to the web-based database to input data and feedback about how pain is managed in the participating site and ‘benchmarking’, comparing the findings with other sites. Sites will be asked to sign a contract that is signed by all medical centres which join PAIN OUT International, outlining rights and obligations of PAIN OUT and the participating site.
Statistical Analysis

The data collected by phone calls or by the patient will be differentiated on the database. These data will be compared and then analysed together if no significant differences are detected.

Incidence of CPSP at 12 months for all types of surgeries analysed will be expressed as mean and confidence interval 95%. We will compare the incidence in various types of surgeries, different centres and countries.

Risk factors of CPSP will be analysed using univariate and multivariate analysis. The most predictive factors will be chosen by fitting a logistic regression model using a forward selection procedure. By combining data from different centres, we will determine most significant risk factors.

Outcome measures

The main outcome measure will be the incidence of CPSP 12 months after surgery. Secondary outcome measures will be incidence of CPSP at 6 months, risk factors of CPSP related to the patient, surgery, anaesthesia and analgesia.
Sample size calculation

We expect that at least 30 ESA CTN sites will be able to participate and recruit 200 patients a year, to a maximum of 6,000 patients, over the one year study period. Since the mean incidence of CPSP is approximately 30%, this will offer an estimated potential number of 2000 patients with CPSP.

Early March 2012, after the first 7 months inclusion, only 20 centres had in fact actively recruited and the percentage of patients followed up at 6 months seemed low. Therefore, we decreased the expected sample to be recruited to 3000 patients at D1, 1000 patients at 6 and/or 12 months with a estimated number of 300 patients with CPSP.

Organisation

Investigators will use questionnaire presently available for Pain Out project in English, German, French, Spanish, Italian, Romanian, Ukrainian, Dutch and Russian. They will supervise data collection, ensure timely data return and act as guarantor for the integrity and quality of data collected.

The principal investigator is a member of the PAIN OUT group and will closely work with the new group of investigators participating in the project on CPSP. His experience with the European PAIN OUT project will be very valuable to organize and coordinate the CPSP project. ESA is supporting this project and will help with administrative coordination to build the European network.

Time scale

The study will last three years with one year and a half for recruitment, one year for follow up and 6 months for analysis.

Funders

The budget of the European Society of Anaesthesiology will help to support coordination.
Protocol History of changes

<table>
<thead>
<tr>
<th>Protocol Version Number and date</th>
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<tr>
<td>Protocol final, v 1.0, 30 Dec 2010</td>
<td>Original version</td>
<td>NA</td>
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<tr>
<td>Protocol v 2.0, Amendment 1, 28 March 2012</td>
<td>Page 1/7:</td>
<td>- Addition of “Sponsor: European Society of Anaesthesiology; Collaborator: University of Jena, Germany; ClinicalTrials.gov Identifier: NCT01467102”</td>
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<td></td>
<td>Page 3/7 Participating centres</td>
<td>- Change in time scale: addition of “and a half” in sentence: ‘We expect that at least 30 ESA CTN sites from Europe will be able to participate and recruit for one and a half year”.</td>
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<td>Page 4/7 Data collection</td>
<td>- Addition of “If the patient has no personal e-mail address it will be possible to propose a follow up by phone call at 6 and 12 months.”</td>
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<td>- Addition of “The data collected by phone calls or by the patient will be differentiated on the database. These data will be compared and then analysed together if no significant differences are detected.”</td>
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<td>Page 6/7 Sample size calculation</td>
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<td>- Addition of “Ukrainian” and deletion of “Hebrew and Swedish”</td>
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