Sensory alterations and immunological changes during the chronification of postsurgical pain

Published: 14-06-2021
Last updated: 21-12-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON54335

Source
ToetsingOnline

Brief title
SCIP-Pain

Condition

- Other condition

Synonym
Chronic postsurgical pain (CPSP)

Health condition

Postoperatieve pijn

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chronic Postsurgical Pain (CPSP), Persistent Postsurgical Pain (PPSP)

Outcome measures

Primary outcome

The main study outcome of interest is the presence of pain with neuropathic characteristics within three months after surgery as assessed by a numerical rating scale (NRS) of 4 or above and a Douleur Neuropathique en 4 (DN4) at a previously defined cutoff score of 4 or higher. Before an endpoint was registered, the presence or absence of pain with neuropathic characteristics must be adjudicated by a consulting pain specialist. The conclusion by the pain specialist whether pain has neuropathic characteristics is regarded as the gold standard.

Secondary outcome

Not applicable

Study description

Background summary

Chronic postsurgical pain (CPSP), pain that newly develops or changes in characteristics after a surgical procedure and persists at least three months after surgery, constitutes a widely underdiagnosed and often poorly treated medical problem affecting 10 to 50 percent of all surgical patients.1,2,3,4 Since pain is a common indication for surgery and surgery itself may result in CPSP, patient selection is of the utmost importance in evaluating a patient for a surgical procedure intended to relief pain.

In a previous study we have developed and validated a postoperative prediction model for the identification of patients at risk for CPSP following a wide range of surgical interventions. The strongest determinant associated with the development of CPSP was the presence of a painful cold two weeks following surgery.5 Since the presence of a painful cold is considered a characteristic of neuropathic pain, this leads to the hypothesis that surgical stimuli may cause sensory alterations in the early postoperative period ultimately resulting in the development of a chronic neuropathic pain state. Although chronic pain may appear to be a disorder of the nervous system, immune cells and their mediators have been identified as important contributors in pain regulation.6
The aim of the present study is to assess the extent of sensory alterations and the role of immunological inflammatory parameters in the transition from an acute into a chronic postsurgical neuropathic pain state. This is important because the efficacy of pain treatment is associated with the pain phenotype based on sensory alterations.7 Combining the information on sensory alterations and the immunological response after surgery may eventually lead to improved pain phenotyping creating opportunities to initiate more mechanism-based treatment regimens for patients at risk for CPSP with neuropathic characteristics.

1. Macrae WA. Chronic post-surgical pain: 10 Years on. Br J Anaesth. Published online 2008. doi:10.1093/bja/aen099
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3. Crombie IK, Davies HTO, Macrae WA. Cut and thrust: Antecedent surgery and trauma among patients attending a chronic pain clinic. Pain. Published online 1998. doi:10.1016/S0304-3959(98)00038-4
4. Macrae WA. Chronic pain after surgery. Br J Anaesth. Published online 2001. doi:10.1093/bja/87.1.88
5. Driel, M.E.C., Rijsdijk M, Baart S HFJPM. Development and validation of a multivariable prediction model for the early prediction of chronic postsurgical pain - In preparation. Published online 2021.
6. Raoof R, Willemen HLDM, Eijkelkamp N. Divergent roles of immune cells and their mediators in pain. Rheumatol (United Kingdom). Published online 2018. doi:10.1093/rheumatology/kex308
7. Forstenpointner J, Otto J, Baron R. Individualized neuropathic pain therapy based on phenotyping: are we there yet? Pain. Published online 2018. doi:10.1097/j.pain.0000000000001088

Study objective

The primary objective is to identify sensory alterations and changes in immunological parameters that are related to the development of chronic pain with neuropathic characteristics in postsurgical patients within three months after surgery.
The secondary objective is to develop a prediction model for the early

identification of patients at risk for CPSP with neuropathic characteristics after elective orthopedic surgery of lower extremities.

Study design

Prospective observational cohort study.

Study burden and risks

Benefit: Postoperative pain will be treated according to routine clinical care. Identified patterns of sensory alterations will not influence pain treatment regimens. Patients, therefore, do not have direct benefit of participation in this study. The obtained knowledge, however, may guide pain treatment regimens and potentially improve treatment efficacy in future patients at risk for CPSP.
Burden/risk: Study participants fill in questionnaires, undergo Quantitative Sensory Testing (QST) measurements (for the identification of sensory alterations) and blood withdrawal (for analysis of immunological parameters) at four different time points (before surgery, directly after surgery (POD0), in a time window between two to four weeks following surgery (POD14) and postoperative day 90 (POD90)). In addition, participants are asked to complete a pain diary daily for the first two weeks after surgery, which will take approximately 5 minutes a day. Completing the questionnaires will take approximately 15 minutes. One QST test session takes approximately one hour to be completed. Blood withdrawal may be painful and takes approximately five minutes to complete.
The health risk of completing questionnaires and undergoing QST testing, both non-invasive, are negligible. The collection of blood via venipuncture or from a previously inserted IV line are low-risk procedures with negligible chance on severe adverse events when performed correctly. The additional health risk of this study is, therefore, classified as negligible. Because the risks of participating in this study are deemed negligible, a request for exemption from the research subject insurance obligation is submitted.
The time burden and the number of site visits associated with this study will be limited in some extent by combining the baseline visit with the appointment at the preoperative assessment clinic. Besides, the QST assessment on POD14 may be combined with a home visit for wound control and removal of stitches. Travel expenses (and parking costs) shall be reimbursed for the extra two scheduled visits.

Risk assessment with regard to the COVID-19 pandemic: Recognizing that the risk of COVID-19 cannot be completely eliminated, this study adds limited risk to the spread of COVID-19 because of the aim to implement research visits in standard care, and the strict adherence to the RIVM policy. The study is compliant with CCMA policy, IGJ policy, EMA guidance and meets the conditions set out by the UMCU. Risks will be reassessed as the situation develops.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- Aged 18 years or older;
- Scheduled for elective orthopedic surgery on lower extremities;
- Able and willing to give written informed consent.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Major cognitive or psychiatric disorders, because QST involves the full

co-operation of participants.
- Problems with communication (language, deafness, aphasia etc.).
- Acute infection confirmed by clinical, laboratory and standard radiological examination, which could confound the assessment of the immunological response.
- Pre-operative definite neuropathic pain condition in the lower extremities according to the updated grading system for neuropathic pain in research and clinical practice by Finnerup et al. in patients scheduled for elective orthopedic surgery of lower extremities, which could confound the assessment of pain processing in the perioperative period.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-09-2021
Enrollment:	150
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	14-06-2021
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	03-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-11-2024
Application type:	Amendment
Review commission:	METC NedMec

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	NL77085.041.21