PJ-008200 Measurements on healthy subjects to design a nociception index

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The primary objective is to measure the effect of nociceptive stimuli on features derived from ECG, ABP, PPG, EEG and facial video recordings, to be used to design an index of nociception. The index of nociception should correlate well with strength...

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

Summary

ID

NL-OMON54413

Source
ToetsingOnline

Brief title
Measurements to design a nociception index

Condition

- Other condition

Synonym
Nociception; Pain

Health condition

meten van pijn bij gezonde vrijwilligers

Research involving
Human

Sponsors and support

Primary sponsor: Philips Patient Monitoring (Philips Medizin-Systeme Böblingen GmbH)
Source(s) of monetary or material Support: In samenwerking met Phillips Research,Philips

Intervention

Keyword: healthy volunteers, nociception, Nociception measurement

Outcome measures

Primary outcome

The primary endpoint of the study is the correlation between the presence of

nociception and measures of nociception.

Secondary outcome

Secondary outcomes are:

- the effect of remifentanil on the correlation between the index of

nociception and the stimulus strengths and related subjective NRS scores.

- the performance of within Philips Research earlier developed vital sign based

(i.e. HRV, BP) algorithms.

- the index of nociception with indices on the market such as ANI.

- the performance of the PainChek facial expressions algorithm for pain

detection

Study description

Background summary

Pain is defined by the International Association for the Study of Pain as *an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*. Nociception is *the neural process of encoding noxious stimuli*.

Nociception during surgery can lead to surgically-induced neuropathic pain (SNPP). SNPP has been estimated to occur in 10-50% of patients. To prevent SNPP, a perioperative strategy would be to continuously block nociception, and for this an objective measure of nociception is necessary.
In clinical practice it is seldom possible to completely block activation of the nociceptive pathways. When spinal or regional anesthesia is not possible, the one of the opioid drugs is administered to counteract the nociceptive signals. At present it is very difficult for clinicians to judge when or if the opioid dose is adequate, and this is a problem because both inadequate and excessive doses have adverse consequences. In adequate doses of opioids are associated with sympathetic activation and hemodynamic instability (tachycardia and hypertension), and possibly an increased risk of SNPP. On the other hand excessive doses are associated with adverse effects such as bradycardia and hypotension, post-operative nausea and vomiting, generalized itching and constipation. Moreover, excessive doses may be associated with opioid tolerance and opioid-induced hyperalgesia which can lead to increased post-operative opioid requirements, and eventually a higher incidence of SNPP.

Nociception measurement and management is a quality indicator for hospitals. Monitoring of nociception in the OR could result in improved patient safety, higher OR throughput, and better patient outcome.

In current clinical practice, anesthesiologists primarily rely on changes in heart rate (HR) and arterial blood pressure (ABP) as a measure of the balance between nociception and anti-nociception (i.e. the dose of analgesic drugs) during surgery. However, with this approach some nociceptive responses may be missed.

There is a need for a continuous, objective nociception index especially for sedated unconscious patients who cannot express their pain levels. There is an increasing number of new nociception/pain/stress indices in the market using a combination of vital signs, using galvanic skin conductance or brain signals or using a combination of different parameters. However, none of these technologies is currently better than BP and HR in predicting nociceptive response and there is definitely room for improvement. In our current study, we aim to use a novel combination of parameters to design a unique nociception index.

Heart rate variability (HRV) is a widely used measure of alterations in sympathetic and parasympathetic autonomic nervous system activity. HRV has been associated with nociceptive stimuli since many years. More recent studies have underpinned the potential value of HRV in nociception measurement.

Another physiological response to nociceptive events is an increase in blood pressure. This has been shown for tonic nociceptive stimuli, as well as short nociceptive stimuli.

Photoplethysmography (PPG) measures local blood volume changes, e.g. at the fingertip. The pre-processing of a patient monitor removes some of the information in a PPG waveform, which is why we chose a recording method that avoids this. The PPG waveform consists of a DC component (i.e. low-frequency variations) and an AC component (higher frequency variations). The AC component has been shown to be relevant for measuring nociception. Various parameters can be derived from the PPG waveform, such as amplitude, area under the curve, and rising slope.

Galvanic skin response is a measure that is used to measure stress, and has also been linked to nociception; either on its own, in combination with heart rate, or in the multi-parameter NoL (nociception level) index.

Nociception can be measured in the brain through electroencephalography (EEG). Evoked potentials (EP) can be observed in the EEG signal after nociceptive stimuli. It is known that peaks in the EP correlate with stimulation strength and subjective experience. The latency of the peaks in the EP are influenced by the time to conduct the signal between the site of stimulation (the calf of the leg) and the part of the brain. Comparing the arrival time of the peaks of the EPs of the different subjects will be influenced by this distance and conductance velocity. With an average conduction velocity of around 10 m/s (Adelta fibers and spinothalamic tract) this can differ ~5ms per 5 cm. The peaks of interests are in the timeframe of 150ms - 400ms with multiple distinct peaks. Comparing the EP peaks latencies and amplitudes or for group analysis it is important to be able to take into account the difference in height (categorical).
Facial expressions have also been studied as a measure of nociception, although interpersonal differences in expressiveness should be considered. An example of an implementation of facial detection for pain detection is the PainChek app. It is currently mostly used in patients with dementia.

With our current study, we can combine all these parameters in a unique dataset that will be used to design a novel nociception index.

Because all these parameters have never been combined for measuring nociception, our current study will serve as a pilot study. To ensure that we have a very well controlled condition for obtaining the data, we will perform our study on healthy volunteers. A study population balanced in age groups and gender is needed, because these factors are known to influence nociceptive response.

When studying nociception in healthy subjects, nociceptive stimuli are given to the subjects. There are various methods of applying these types of stimuli, which are well described in the literature. Nociception can be induced by either phasic or tonic nociceptive stimuli, phasic nociceptive stimuli are short stimuli of which the stimulation strength is well controllable which gives the opportunity to administer different stimulus levels (painful or

non-painful). Tonic stimulus is a persistent nociceptive stimulus.

By applying more than one type of stimulus, a more accurate representation of nociception can be obtained. Electrical stimulation activates the nociceptive nerve fibers directly surpassing the receptors, and has the advantage of short and fast pulses making it suitable for studying evoked potentials in the EEG, see for example. Thermal stimulation pulses are less instantaneous, but do not bypass the receptors as the electrical stimulation does. Both electrical and thermal are phasic stimuli giving the opportunity to stimulate at different stimulations levels making it possible to test the index for both non-painful as painful levels. For a more gradual nociceptive stimulus, the cold pressor test is a well-established tonic stimulation method.
Next to relationship between the measured parameters and stimulation modalities and stimulus strengths also the relationship between these and the subjective score is of interest. Subjective pain experience can be measured by means of the so called Numeric Rating Scale (NRS). This is a scale from 0 till 10 with 0 meaning no sensation and 10 the pain tolerance level.

An objective measure of nociception that is to be used during surgery, should not lose its value when analgesia is used. A commonly used analgesic during surgery is remifentanil. Remifentanil is also used in the literature to assess the value of a measure of nociception during analgesia use. Adding remifentanil to our protocol gives a first, important insight into the value of the new nociception index during surgery.

Study objective

The primary objective is to measure the effect of nociceptive stimuli on features derived from ECG, ABP, PPG, EEG and facial video recordings, to be used to design an index of nociception. The index of nociception should correlate well with strength of nociceptive stimulus and subjective NRS score.

The secondary objectives are to:
- Analyse the effect of remifentanil on the correlation between the index of nociception and the stimulus strengths and related subjective NRS scores (remifentanil is standard in surgery care, is fast acting, and often used in other studies that research nociception).
- Evaluate the performance of within Philips Research earlier developed vital sign based (i.e. HRV, BP) algorithms.
- Benchmark the index of nociception with indices on the market such as ANI (Analgesia Nociception Index).
- Evaluate the performance of the PainChek facial expressions algorithm for pain detection

Study design

This clinical investigation is designed as an observational pilot study, because a unique dataset needs to be obtained to design an index of nociception.

Study burden and risks

The risks of participation in this study are assessed to be acceptable (negligible).

The disadvantages of participating in the study can be
- the development of possible side effects;
- Possible inconveniences due to the measurements in the study.
- time consuming of about 5 hours;

There is no clinical benefit for the participating healthy volunteer

Contacts

Public
Philips Patient Monitoring (Philips Medizin-Systeme Böblingen GmbH)

Hewlett-Packard-Straße 2
Böblingen 71034
DE
Scientific
Philips Patient Monitoring (Philips Medizin-Systeme Böblingen GmbH)

Hewlett-Packard-Straße 2
Böblingen 71034
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Inclusion criteria

1) Age between 18 and 65 years old
2) ASA I Healthy subjects
3) BMI < 35
4) Females should be using contraception

Exclusion criteria

1) Pregnancy (pregnancy test before start protocol, if female, with the exception of post menstrual women)
2) Smoking
3) Alcohol abuse
4) Medication that influeunces the central or peripheral nervous system, or the cardiovascular system
5) Drug use (drug test before start protocol)
6) Raynaud's disease (poor blood circulation)
7) Scleroderma, Dupuytren*s Contracture, or other Rheumatology issues
8) Depression and/or anxiety (the Hospital Anxiety and Depression Scale (HADS) questionnaire is given before the start of the protocol. Subjects with a score greater than or equal to 11 are excluded)
9) Food eaten in the 6 hours before the test
10) Fluid intake within less than 2 hours of the planned start of experimentation
11) Use of caffeinated beverages in the 12 hours before the test
12) Use of caffeinated food (e.g. chocolate) in the 6 hours before the test

COVID-19 additional Exclusion criteria:
13) Currently displaying COVID-19-related symptoms, namely a fever, cough and/or difficulty breathing
14) Having been positively tested as infected with COVID-19 in the past 14 days
15) Travelled to or from high risk COVID-19 areas in the past 14 days
16) Been in contact with a (suspected) COVID-infected person in the past 14 days

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-06-2022
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	03-02-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	27-02-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 28208

Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL77088.100.21
Other	NL9366
OMON	NL-OMON28208