A Prospective Study Evaluating a Pain Assessment Tool in Postoperative Environment: A Protocol for Algorithm Testing and Enhancement

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Abstract

Background: Pain assessment is critical to the optimal treatment of pain. There is a high demand for accurate objective pain assessment for effectively optimizing pain management interventions. However, pain as a multivalent, dynamic, and ambiguous phenomenon is difficult to quantify, particularly when the patient's ability to communicate is limited. The "gold standard" of pain intensity assessment is self-reporting. However, this unidimensional model is disparaged for its oversimplification and limited applicability in several vulnerable patient populations. Researchers have attempted to develop objective pain assessment tools through analysis of physiological pain indicators, such as Electrocardiography (ECG), Electromyography (EMG), Plethysmography (PPG), and Electrodermal Activity (EDA). However, pain assessment by using only these signals can be unreliable, as there are various other factors that alter these vital signs and the adaptation of vital signs to pain stimulation varies from person to person.

Objective: This paper aims to develop an automatic and versatile pain assessment tool algorithm for detection and assessment of pain in a reliable and objective way in non-communicative patients through observational data collection by wearable technologies, measuring facial EMG, ECG, PPG, and EDA.

Methods: This study was planned to be done in three different phases: (1) Evaluation and Test of usability, utility, and accuracy of the new pain assessment tool in 30 healthy working-age volunteers, (2) Further development and research of a pain assessment tool in patients likely experiencing mild to moderate pain, and (3) Conduct a trial to assess the effectiveness of the whole platform in uncommunicative patients at two different sites which serve as the sites of both intervention and control group. Currently available state-of-the-art standard sensors were used to measure bioelectrical EMG signals as well as changes in heart rate, respiratory rate, and oxygen saturation. Based on the results, the pain assessment tool was further developed and reconstituted with modern wearable sensors, devices, and algorithms. In this paper, we focus on the second part of the study. HUMAN RESEARCH PROTECTIONS Application for IRB Review (APP) was approved for this paper.

Results: The development of the pain assessment tool is calculated to be ready in early 2020. Preliminary results will be ready for publication from Fall 2019.

Conclusions: This paper is about the second phase of research on multimodal signals including facial muscle electrical activity, cardiac electrical activity, and electrodermal activity as indicators of pain. This paper will allow testing the smart pain assessment tool in uncommunicative patients in a multicenter, multinational setting in California/USA and Turku/Finland to promote pain management of patients and enhance the safety and quality of care.

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Abstract

Background: Pain assessment is critical to the optimal treatment of pain. There is a high demand for accurate objective pain assessment for effectively optimizing pain management interventions. However, pain as a multivalent, dynamic, and ambiguous phenomenon is difficult to quantify, particularly when the patient's ability to communicate is limited. The "gold standard" of pain intensity assessment is self-reporting. However, this unidimensional model is disparaged for its oversimplification and limited applicability in several vulnerable patient populations. Researchers have attempted to develop objective pain assessment tools through analysis of physiological pain indicators, such as Electrocardiography (ECG), Electromyography (EMG), Photoplethysmography (PPG), and Electrodermal Activity (EDA). However, pain assessment by using only these signals can be unreliable, as there are various other factors that alter these vital signs and the adaptation of vital signs to pain stimulation varies from person to person. Objective pain assessment using behavioral signs such as facial expressions has recently gained attention.
Objective: This paper aims to further development and research of a pain assessment tool in patients likely experiencing mild to moderate pain through observational data collection by wearable technologies, measuring facial EMG, ECG, PPG, and EDA.
Methods: This protocol focuses on the second phase of a larger study. It is about the second phase of research on multimodal signals acquisition including facial muscle electrical activity, cardiac electrical activity, and electrodermal activity as indicators of pain and building predictive models. Currently available state-of-the-art standard sensors were used to measure bioelectrical EMG signals as well as changes in heart rate, respiratory rate, and oxygen saturation. Based on the results, the pain assessment tool will further be developed and reconstituted with modern wearable sensors, devices, and algorithms. *HUMAN RESEARCH PROTECTIONS Application for IRB Review (APP)* was approved for this paper.
Results: The development of the pain assessment tool is calculated to be ready in early 2021. Preliminary results will be ready for publication from Fall 2020.
Conclusions: The current study, will help in further development and research on an objective pain assessment tool for monitoring patients likely experiencing mild to moderate pain.

Keywords: Pain Assessment; Recognition; Health Monitoring; Wearable Electronics; Machine

Learning; Multi-Modal

Introduction

Pain is the most common reason for patients to seek medical care and is associated with many illnesses[1]. There is a high demand for tools to support patient's pain assessment in clinical context. Tools are needed especially when patient's own opinion is difficult to reach. Assessment of pain is particularly difficult when the ability of a patient to communicate is limited (e.g., during critical illness, infants and preverbal toddlers, patients under sedation or anesthesia, persons with intellectual disabilities, and patients at the end of life)[2]. At present, there is a wide variability in how pain is assessed and managed at bedside, and the prevalent practices remain suboptimal[3]. Inadequately treated pain has major physiological, psychological, economic, and social ramifications for patients, their families, and society[4]. Under-treatment of pain could result in many adverse effects and other complications and may evolve into chronic pain syndromes. It could also cause delayed discharge or prolonged recovery, which may incur higher healthcare costs and more patient suffering[5]. Overtreatment of pain, on the other hand, may result in unintended adverse consequences such as acute respiratory complications or long-term complications such as opioid addiction. These issues are particularly pronounced for non-communicative patients who are unable to articulate their experience of pain[6].

Automated and continuous pain intensity assessment for poorly communicating patients can enable timely treatment, reduce the monitoring burden on clinicians, and contribute to optimizing the use of analgesics and managing side effects and complications[7]. As pain intensity current knowledge is difficult to quantify[8], the “gold standard” of pain assessment is self-reporting using tools such as the Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS)[9]. These tools are rife with deficits, which are even more pronounced in vulnerable patient populations[6,10].

The state-of-the-art automatic and objective pain intensity assessment techniques in the literature utilize physiological data, which monitors the changes in patients’ physiological data such as Electromyography (EMG), Electrocardiography (ECG), Photoplethysmography (PPG), and Electrodermal Activity (EDA) to identify autonomic nervous system reactions to pain. One of the most well-known pain indicators is facial muscle activity. The facial nerve controls voluntary and involuntary activity of the facial muscles. The involuntary control of facial muscles is both protective and emotional, signaling the experience of pain. Other objective pain assessment tools include Surgical Pleth Index (SPI, formerly Surgical Stress Index SSI) which are based on analysis of PPG waveform and heart rate. Similarly, analysis of skin conductance has been used as a surrogate for pain in clinical situations[11].

Wearable technology is a promising paradigm to integrate several technologies and communication solutions[12,13]. The aim of this research project is to develop an automatic and versatile pain assessment tool algorithm for detection and assessment of pain in a reliable and objective way in non-communicative patients. The final objective of the research project is to develop a smart pain assessment tool to detect and assess pain employing behavioral and physiologic indicators for a wide range of users/patients from infants to elderly people who are unable to communicate normally.

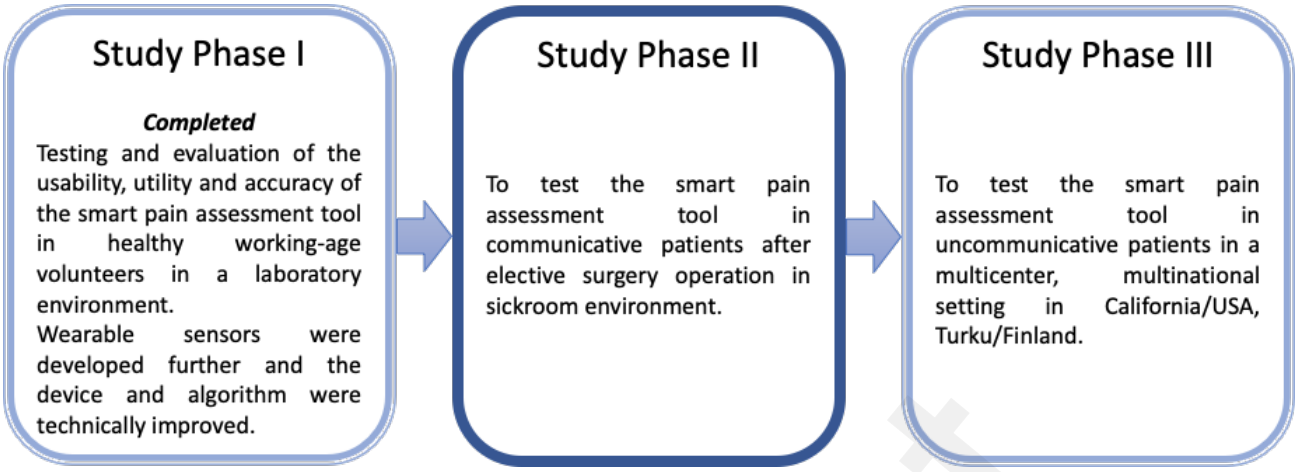

Figure 1. The study design of the pain assessment tool

The main research project consists of three study phases which are described in Figure 1. The phase I of the research project focused on developing pain assessment techniques in voluntary healthy adults. In Study Phase I, usability, utility and accuracy of the new pain assessment tool was evaluated and tested in 30 healthy working-age volunteers. Currently available state-of-the-art standard sensors were used to measure bioelectrical EMG signals as well as changes in heart rate, respiratory rate, oxygen saturation and galvanic skin response. Based on the results, the pain assessment tool was further developed and reconstituted with modern wearable sensors, device, and algorithm.
The Study Phase II, current study, includes the further development and research of a pain assessment tool in patients likely experiencing mild to moderate pain. Finally, the last phase is to conduct a trial to assess the effectiveness of the whole platform in uncommunicative patients at two different sites which serve as the site of both intervention and control group. In the intervention and control patients, continuous pain intensity assessments will be collected by the sensors embedded in the facial patch worn by all study patients.

Methods

Study Design

This protocol focuses on the second phase of a larger prospective observational data collection study to collect training data from patients likely experiencing mild to moderate pain with the local IRB approval (HS# 2017-3747). All study phases of the pain assessment tool are described in Figure 1.

The IRB approval is to recruit 30 subjects which are selected from the Acute Pain Service patient (APS) list at UCI Medical Center (UCIMC). The APS unit at UCIMC serves over 100 participants weekly, enabling the lead Doctor of Medicine (M.D.) to recruit patients for this study. Primary demographic data from each patient will be collected which includes height, weight, body mass index, and sex. Approximately 30 minutes of continuous biosignals (EMG, ECG, and EDA) data will be collected from the participants. This 30-minute period will be separated into two parts: Control (baseline pain) and Experimental. Each part will consist of 2-3 challenge intervals in an attempt to capture pain perception before, during, and after stimulus with appropriate rest periods to make the statistical analysis more powerful. In the control part, Transcutaneous Electrical Nerve Stimulation (TENS) unit [14] will be used to obtain the baseline pain of the patient by placing TENS on the subject's forearm and consistently prompting for NRS pain scores. We believe it is prudent to provide some level of baseline assessment over and above the patient's existing post-surgical pain to attempt

to find a baseline of pain for comparison among subjects. Therefore, we used the TENS unit as a manner of standardizing the patient threshold for experiencing pain and also as a way to keep the data consistent with the previous phase of the study conducted on healthy volunteers. In the experimental part, patients will be engaged with soft activities (such as walking, coughing, seating, lifting legs to name but a few) that may cause pain sensation. The subject's experience of pain will be recorded using NRS. The NRS for pain is a unidimensional measure of pain intensity and a segmented numeric version of the VAS in which a respondent point to the number on the NRS, a whole number (0–10 integers), that best represents the intensity of their pain [15]. The usual format is a horizontal bar or line [16]. Similar to the pain VAS, the NRS is anchored by terms describing pain intensity extremes [16–18]. We expect to find solutions from multiple parameters that are robust in response to different acute pain cases or study designs. All protected health information should be redacted prior to data analysis.

Participants

The prospective study will be conducted at the UCIMC in Orange County, CA, USA. The primary study population comprises adults with an age range of 18-89 years. The maximum number of patients to be consented or reviewed/collected, including withdrawals and screen failures, is 30, and we expect 20 to complete the study.

Eligibility Criteria

Participants who are enrolled on this UCI protocol must meet the following criteria: (1) age>18-year, (2) patients who will be consulted by the Acute Pain Service, (3) ability to communicate, (4) written informed consent, and (5) healthy, intact facial skin. Participants will be excluded if they have (1) any diagnosed condition affecting cognitive functions (dementia, psychosis), (2) hand deformities that prevent the sensor from being placed, (3) any diagnosed condition affecting the central nervous system, facial nerves or muscles, or (4) significant facial hair growth in the area where the sensors will be attached.

The study team must consider the natural variation in caseload (such as trauma and elective procedures) specific to our institution’s region, coupled with the fact that the recovery period is different for each patient. All candidates considered for enrollment universally will be experiencing post-operative pain during their hospitalization, and all will be receiving analgesic treatment. The study team ensures that patient safety will not be compromised while maintaining regulatory compliance, and future studies will be aimed at multi-center studies with a larger, diverse sample size to support generalizability.

Recruitment

After IRB approval, the research team will screen the rounding list of the Acute Pain Service at UCIMC medical records, which they have access, to determine subject eligibility using the protocol inclusion/exclusion criteria. The patients' anesthesiology MD will approach patients directly about study participation. The study procedure will be continued if the patient shows interest and is suitable for the study (inclusion and exclusion criteria); then, the study MD will explain the study in detail. The study subject will be given a consent form in which the patient has a day to study. On the following day, the study MD will follow up with the patient if they still want to participate in the study. If the patient changes their mind and does not want to participate in the study, the study will be discontinued for this patient. If the patient is still willing to participate, the study subject enrollment

log will be updated accordingly. During the study, the subject's experience of pain intensity will be recorded using NRS.

Informed Consent Procedures

Potential participants will get both oral and written information about the details of the study in their private room; then, they have 24 hours to consider whether to consent. No member of the study team has any disclosable conflicts of interest. All subjects are encouraged to discuss study participation with family and friends before consenting. The patient will be enrolled in the study only after one of the investigators reviews the consent form with the patient, ensuring the patient has understood the study, has answered all questions and written informed consent is obtained. They are also informed about their right to withdraw from the study at any time. Subjects are informed that their participation is voluntary and would not impact their patient care.

Clinical Trials

iHURT is a system that tracks changes in the activity of facial muscles (i.e. changes in facial expressions) and simultaneously uses physiologic signs such as heart rate, heart rate variability, respiratory rate and EDA as adjuvant measures as we attempt to develop an algorithm for pain assessment in hospitalized patients. The technology used in this paper to capture the aforementioned signals includes the following components:

1) Eight-channel biopotential acquisition system for EMG and ECG recording

   EMG and ECG are both biopotential signals captured from the skin surface. The system used to collect them were developed in our previous work[14]. The system includes commercially available electrodes (e.g., in 24mm diameter), electrode-to-device lead wires, an ADS1299 based portable device, and a computer software receiving streaming data from the portable device. The small analog potentials sensed from the skin surface is amplified (max gain: 24), digitized, and the raw data of each channel at the rate of 500 samples per second is sent to the computer software through Bluetooth. The software visualizes the waveforms and save the raw data into files.

   The device is configured to work in single-ended mode, or is called monopolar electrode configuration, where the potential in each channel is measured between the electrode on the target site and the common reference electrode. The common reference electrode is placed on neutral bony area behind the ear. Due to this reason, two channels are used to collect lead I ECG, as illustrated in Figure 2. One channel is to measure the potential between ECG - right arm (RA) and reference (R), and the other channel is to measure the potential between ECG - left arm (LA) and R. Five channels are for facial EMG measurement, where the activities of five facial muscles, frontalis, corrugator supercilii, orbicularis oculi, levator labii superioris and zygomaticus major are monitored. The electrodes placement follows the electromyographic research guidelines[15].

2) Empatica E4[16] for EDA and PPG recording
   As a sensitive and convenient measure of indexing changes in sympathetic arousal associated with emotion, cognition and attention, EDA has been widely used in psychological studies[17] and in some commercial devices. As a non-invasive and low-cost measure of monitoring changes in blood volume, PPG has been widely used health domain studies.

To monitor the EDA and PPG, we use the commercially available Empatica E4 wristband. The wristband will permit subjects to maneuver more easily as it will not impede their movements in any way and will reduce the time of each patient encounter as it is considerably easier to position on the patient. The wristband has internal memory which allows the ability to record up to 36 hours of data and allows for wireless data transmission. The E4 wristband is rechargeable and has a charging time of less than 2 hours. The E4 wristband includes an EDA sensor, which measure the constantly fluctuating changes in certain electrical properties of the skin. This device can also give non-invasive monitoring of blood volume pulse PPG in real-time through Green and Red LEDs.

3) TENS unit device (FDA cleared Class II OTC HealthmateForever YK15AB electrotherapy device[18])

TENS unit works by delivering small electrical impulses through electrodes that have adhesive pads to attach them to a person's skin.

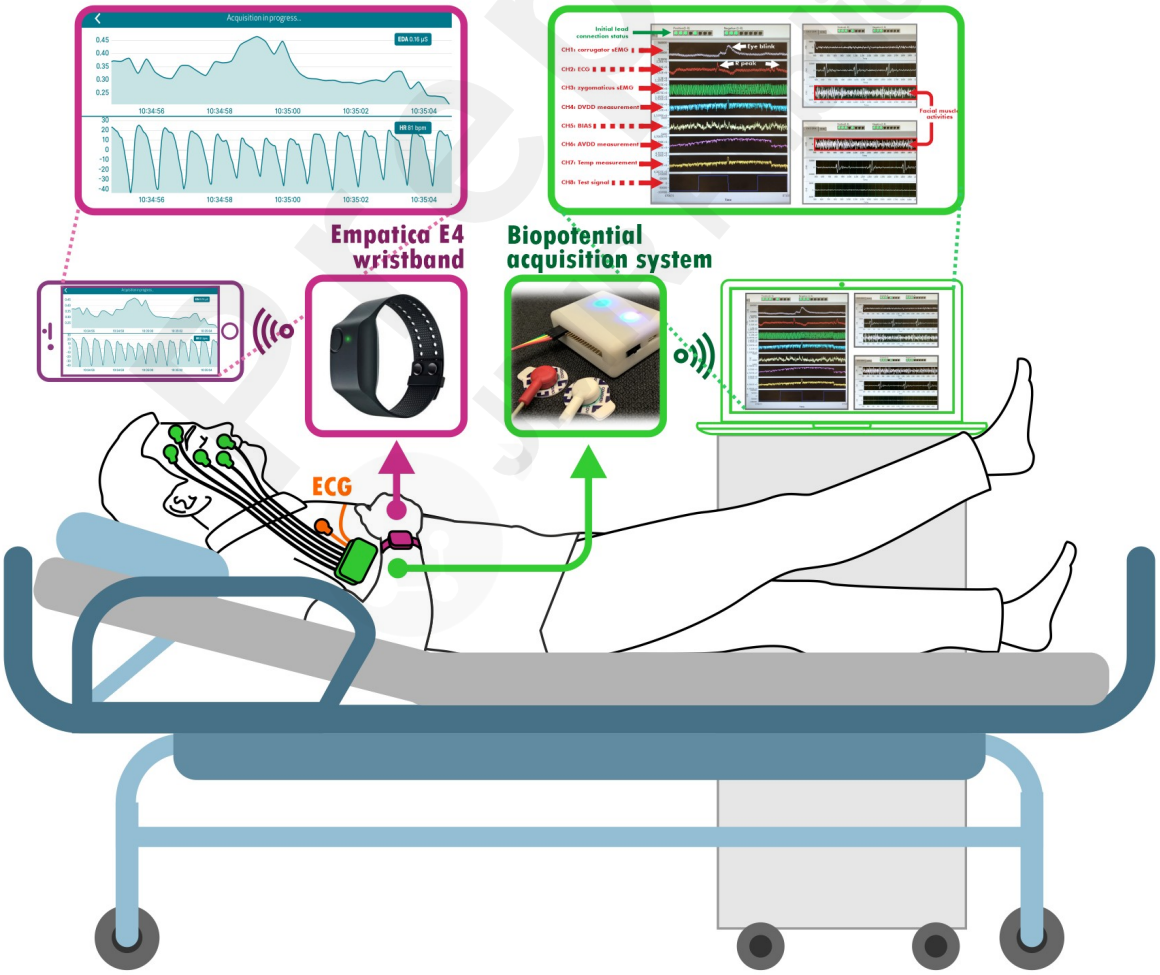

Figure 2. The biopotential acquisition system mounted on the patient

Procedures

All subjects will have their medical history reviewed at the time of the screening. These subjects will be selected from the Acute Pain Service patient list at UCIMC. Upon passing the eligibility criteria, the principal investigators, co-researcher, or research personnel under the supervision of the PIs will approach the patients at UCI Douglas Hospital. The study team will introduce the study to the patients and will leave an informed consent form to review. Study team members will follow up with the patient the day after study introduction to answer any questions and get the consent form from the patient.

After subject consent is signed, a study team member will explain what will happen in the next 30 minutes, how to report pain level, and what NRS is, and will demonstrate how TENS unit works and the fact that it is not harmful. Then, the following components will be placed on the subject: (1) 8 leads of the EMG+ECG, (2) Empatica E4 sensor, and (3) TENS unit on the contralateral (non-IV) arm.

Biopotential acquisition device will be connected to the study analyst laptop and the Empatica E4 will be connected to study analyst iPhone both over Bluetooth. Data recording will begin after the study subject, Clinic Researcher and Study Analyst are ready. Recording of electronic measurements begins. Start of the period is marked on the computer and on the CRF. Data from the sensors will be collected for a maximum time period of 30min. In addition, patients will be asked to complete the following parts:

- **Part 1:** Once the study equipment is placed on the subject, a member of the study team will turn on the TENS unit device while the patient is sitting. Patients will be asked to slowly increase the TENS unit level on the contralateral (non-IV) arm to the highest tolerable level for them, rest for at least 10s, and then decrease it to level 0, including additional rest between TENS challenges. At each point the study team member will ask for the NRS pain score. During this period, the other devices will be simultaneously collecting physiological data.

- **Part 2:** Meanwhile, the patient is resting in the transition between the control and experimental part, the TENS unit will be disconnected. Then, patients will be engaged with soft activities (e.g., walking, coughing, seating, lifting legs, etc.) that may cause pain sensation wearing the non-invasive devices connected excluding the TENS device. At each point (before, during, after activity performance), the study team member will ask for the NRS pain score. During this period, the other devices will be simultaneously collecting physiological data.

  Each domain will consist of 2-3 challenge intervals in an attempt to capture pain perception using NRS before, during, and after stimulus with appropriate rest periods to make the statistical analysis more powerful. Subject's experience of pain will be recorded using NRS. During this period, the other devices will be simultaneously collecting physiological data. Data acquisition software will be used to capture data from the device and sensors.

Software for data display and store

As mentioned above, two devices transmit data wirelessly through Bluetooth and one via serial wired USB. Computer with Bluetooth USB adapters receive from these sensor nodes. A

software is developed in Windows for adding time stamps, real-time waveform plotting, and data save. The waveform plotting function can ensure data validity checking during measurement. Raw data will be saved for off-line processing and analysis.

Algorithm for pain data analysis

The pain intensity assessment algorithm will be developed after the data collection phase, including basic signal pre-processing and machine learning algorithm. The designed algorithm will be built based on preliminary algorithm from phase I of the study and will be verified and compared within the two databases.

Statistical Analysis

Sample Size Calculation

Figure 3 illustrates how multidimensional data obtained during phase I of the study can be processed and reduced to two dimensions for visualization by principal component analysis (PCA)[19] to demonstrate different pain levels.

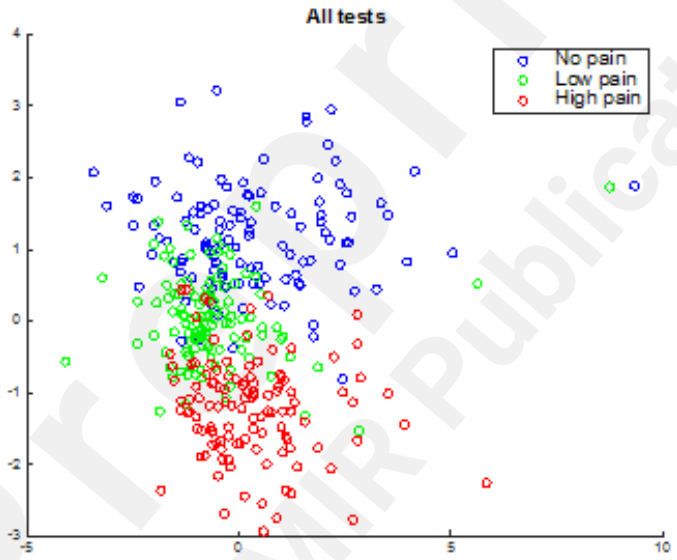

Figure 3. PCA of different pain levels

Figure 4 shows receiver operating characteristic (ROC) curves of multidimensional data classification with artificial neural network[20]. The results are consistent with the data visualization in Figure 3, where moderate/severe pain (shown in red) can be differentiated from no pain samples (shown in blue). A comprehensive machine learning analysis on the Phase I data is available in [21]. Our Phase I results show %76.7 accuracy when we used leave one subject out cross-validation showing that the data can be generalized. Meanwhile, solutions for remote pain assessment were also explored in this phase. An e-health system was designed and implemented, consisting of biosignal measurement & wireless transmission device, online data processing on cloud and remote data presentation webpage for caregiver[21].

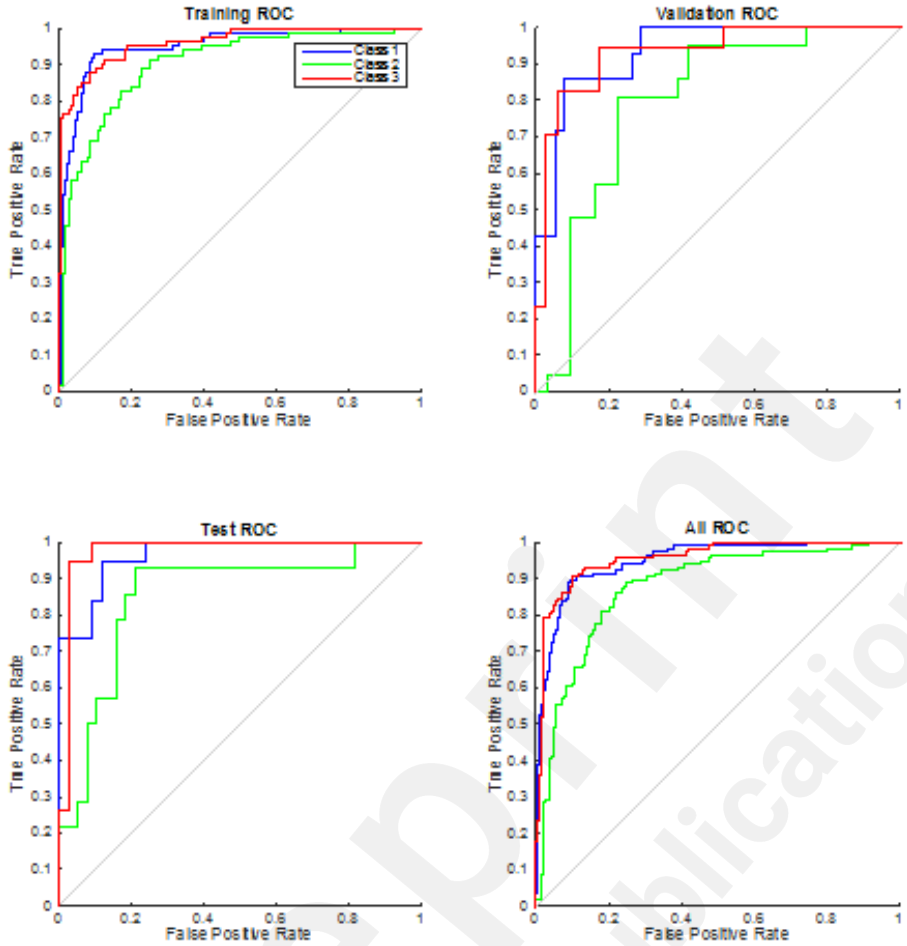

Figure 4. ROC of training, validation, and test datasets

For the Phase II, we attempt to further improve the accuracy and identify proper personalization methods based on the demographic data, profile of the patient when admitted into the hospital, and the biosignals collected from the patients. For the prospective study, subjects who comply with the inclusion criteria will be recruited. The study team will take into account the attrition rate and will have a maximum enrollment of 30 subjects. This sample size has been calculated taking into account the ROC-analyses from the previous phase results[21,22].

Planned Analysis

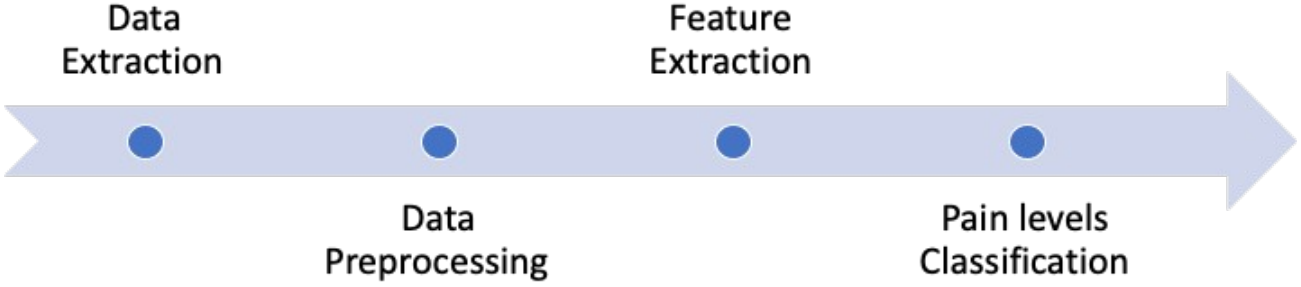

Figure 5. Block diagram of planned analysis

A multi-modal software tool performing signal processing, data fusion, and machine learning for pain assessment and classification will be designed based on the processing flow developed from study phase I.

The analysis of pain can be broken down into the following stages: data pre-processing, filtering, feature extraction, and classification. Different modalities collected from patients such as EMG, ECG, and EDA signals are labelled with patient's self-report pain level. Once these raw signals are extracted, their corresponding timestamps are used to help synchronize the data and better understand the changes in physiological signs when pain is induced.

The next step is to digitally filter out the noise produced during data collection. Noise can be caused by multiple sources. For example, motion artifacts, baseline wander, and power channels are all common sources of noise in a clinical setting. The low and high frequency noise is digitally filtered using a Butterworth filter and the necessary frequencies are allowed to pass through using a bandpass filter.

For the optimal classification performance, features will be extracted from multiple signal domains and approaches, for example, statistical features and entropy extracted from signal time domain and frequency domain[22]. The extracted multiple features will be further optimized in combination to reach a balance between classification performance and computation complexity. These features are receptive to changes in pain stimuli and therefore are good factors in determining the pain levels of an individual.

Finally, once these features and their corresponding pain labels are obtained, we can use machine learning techniques to train models based on this data. Furthermore, we automatically classify and predict the pain levels of any future patients using this existing model.

Outcome Variables

The final outcome of this paper is the prediction of the pain levels of the patients based on metrics such as accuracy, sensitivity, specificity, and area under curve with respect to self-report NRS of the patients as the reference (gold standard).

Results

We have already started implementing the protocol, and we are in the middle of the data collection, we decided to exclude the progress we have already made. We expect the analyses to be completed early in Fall 2020 and then publish them. Dataset will be available for further research in early 2021.

Discussion

Contributions

This is the first protocol collecting physiological signals from postoperative pain for automatic pain assessment development. Existing databases target on several types of pain, for example, chronic pain[23], neonatal pain[24], shoulder pain[25], or experimental acute pain[26–28], but without covering postoperative pain. The proposed methods and database fill the gaps in clinical acute pain in developing and testing automatic pain assessment tools.

The proposed data collection protocol is for multimodal development, similar to some of the aforementioned databases[23,26–28]. However, it includes a different variety of signal sources for the development compared to the existing databases, covering more than indices for autonomic nervous activities such as ECG, EDA, and PPG and non-verbal pain behaviors such as facial expressions and body postures possibly. Thus, the proposed method could provide a new fusion

angle, merging prior knowledge for each signal (eg, [29,30]) and bringing new exploration.

Strengths

Although the data collection focuses on postoperative pain, controllable experimental pain stimulus was included as one pain stimulus, which was separated induced from the movement inductions. The benefits of the design are twofold. On the one hand, the physiological responses to each stimulation can be compared to each other in terms of similarity and difference within the database. On the other hand, it connects this paper to previous studies using experimental pain stimulation only, where pain threshold (stimulus intensity at which pain begins to be felt) and pain tolerance (the maximum pain intensity a person is able to tolerate) were mainly used as pain self-reports.

Limitations

The main limitation is the presence of noise (or incorrect labels), making the machine learning difficult. Although a certain level of noise has been shown to be positive in order to obtain a more tolerant and robust algorithm, given the real day-to-day data, the noise ratio must be low so that this does not interfere with the learning of the machine. In our case, noise comes mainly from the cognitive difference in pain levels and motion artifacts. These artifacts can be from several sources such as the movement of the electrodes on the face while the patient is talking.
Another limitation of this protocol is that some physiological parameter changes (eg, elevated heart rate) could result from a compound reaction to both pain stimulus and the motion itself. However, these two factors cannot be separated within the same patient, ie, moving without causing any pain. One amendment could be recruiting healthy controls to make the same motions and observe the physiological parameter response difference from postoperative patients.

Acknowledgements

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Conflicts of Interest

None declared.

Abbreviations

ECG: Electrocardiography
EMG: Electromyography
EDA: Electrodermal Activity
PPG: Photoplethysmography
VAS: Visual Analogue Scale
NRS: Numeric Rating Scale
SPI: Surgical Pleth Index
SSI: Surgical Stress Index
UCIMC: University of California Irvine Medical Center
APS: Acute Pain Service
TENS: Transcutaneous Electrical Nerve Stimulation
PCA: Principal Component Analysis
ROC: Receiver Operating Characteristic

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Supplementary Files

Figures

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