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CLINICAL RESEARCH

The effect of emotional stressors on postoperative skin conductance indices: a prospective cohort pilot study☆

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KEYWORDS
Emotional stressors;
Intellectual task;
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Abstract
Background: Skin conductance response reflects the activity of the sympathetic nervous system and is used to measure acute pain. This pilot study examines correlations of skin conductance response with emotional stressors postoperatively.
Methods: The correlation of skin conductance response with pain, anxiety, nausea and intellectual task performance was analyzed in postoperative patients.
Results: Significant correlations were observed between anxiety and pain during physical activity on both postoperative day 1 and 2. No significant correlations were found between skin conductance response versus mild pain, nausea, anxiety or intellectual task performance.
Conclusion: This pilot study suggests that when the pain is well-controlled in the early postoperative period, skin conductance response monitoring may not be influenced by other emotional stressors.

PALAVRAS-CHAVE
Estressores emocionais;
Tarefa intelectual;
Dor pós-operatória;
Condutância da pele

Efeito dos estressores emocionais nos índices de condutância cutânea no pós-operatório: estudo piloto de coorte prospectivo

Resumo
Justificativa: A variação da condutância da pele reflete a atividade do sistema nervoso simpático e é usada para avaliar dor aguda. Este estudo piloto examinou as correlações entre a variação da condutância da pele e estressores emocionais no pós-operatório.

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Método: A correlação entre a variação da condutância da pele e dor, ansiedade, náusea e desempenho de tarefa intelectual foi analisada em pacientes no pós-operatório.
Resultados: Correlações significantes foram observadas entre ansiedade e dor durante atividade física nos dias 1 e 2 pós-operatórios. Não foram encontradas correlações significantes entre a variação da condutância da pele e dor leve, náusea, ansiedade ou desempenho de tarefa intelectual.
Conclusão: Este estudo piloto sugere que, quando a dor é bem controlada no pós-operatório inicial, o monitoramento empregando a variação da condutância da pele pode não ser influenciado por outros estressores emocionais.

Introduction

The early assessment and treatment of pain are accepted as mandatory standards for appropriate patient care.[1] This directive has improved pain management and patient satisfaction, but it has also increased the incidence of opioid-related side effects, including respiratory depression with fatal outcomes.[2] Various pain assessment tools, such as the Numeric Rating Scale (NRS), have been developed and validated.[3] The self-report of pain is defined as the gold standard even though it may be influenced by anxiety, level of education, employment status, age and sex.[4] The NRS is reported to be more clinically applicable than the visual analogue scale (0–100 mm), specifically in elderly and in patients on opioids.[3] The current self-report assessment tools cannot be used effectively in certain patient populations unable to report their pain, such as cognitively impaired patients, sedated patients and children. In this group of patients, there is a risk of inadequate or overtreatment of pain, which in turn may lead to negative outcomes. When patients cannot report their pain, observational and physiological parameters are used. Therefore, a monitor to objectively assess the pain would be clinically valuable. An ideal monitor would be non-invasive, fast-reacting, continuous (real-time), sensitive and specific to assess pain.

Skin sympathetic activity influences skin conductance indices, and this can be measured by a non-invasive monitor. The Skin Conductance Algesimeter (SCA) measures skin sympathetic nerve activity mirrored by variations in Skin Conductance Responses (SCR) on the palmar side of the hand.[5] Each time the skin sympathetic nervous system is activated, the palmar and plantar sweat glands fill up with sweat. Due to electrolytes present in sweat, the skin resistance decreases and the skin conductance increases. The reabsorption of the sweat in the sweat glands reverses this process and leads to a decrease in skin conductance.[5] SCR can be monitored by SCA and this response is directly linked to skin sympathetic nerve activity.[5] The number of SCR is a measure of how often the skin sympathetic nerves fire. The numbers of SCR increase during emotionally stressful stimuli like moderate-severe pain,[6–9] and this is different than the painless or mild pain conditions.

The primary aim of this study was to examine the correlation between assessment of pain by using SCR and acute postoperative pain scores (NRS), and our secondary aim was to evaluate the correlation of SCR with other emotional stressors in the postoperative period. The influence of these factors on skin conductance indices in the postoperative setting is largely unknown. Our hypothesis was that SCR would not show a significant positive correlation with emotional stressors other than pain, thereby will increase the specificity of SCR as a viable physiological monitor for the assessment of moderate-severe pain postoperatively.

Material and methods

Subjects

Among the total of 76 patients scheduled for Total Hip Replacement (THR) or total knee replacement (TKR), age 18–85, who met the basic inclusion criteria, 67 patients were deemed eligible. Of the 67 patients, 17 were excluded from analysis. A STROBE flow-chart of participants is presented in Figure 1 indicating the recruitment of individuals. The remaining 50 patients undergoing either THR or TKR procedures were enrolled. The ClinicalTrials.gov number was NCT02408263. The data were collected from November 1, 2010 to July 27, 2011.

Inclusion criteria were patients with age 18–85, scheduled for primary unilateral THR or TKR surgery, and who were able to provide written informed consent to participate in this study.

Exclusion criteria were bilateral procedures, patient communication barriers, diagnosis of dysautonomia, disorders of sympathetic dysfunction (e.g. Raynaud disease) disorders of sweating, unable to apply skin conductance contact electrodes at the usual area of skin conductance measurement, pacemaker/automated implantable cardioverter-defibrillator, autonomic neuropathy, history of contact reaction to adhesive tapes, with the history of chronic opioid use as defined by use of long acting opioid medication for more than 6 months and use of anticholinergic agents.

Perioperative information was collected by retrospective chart review. Patient demographics, age, gender, race, Body Mass Index (BMI), comorbidities, American Society of Anes-

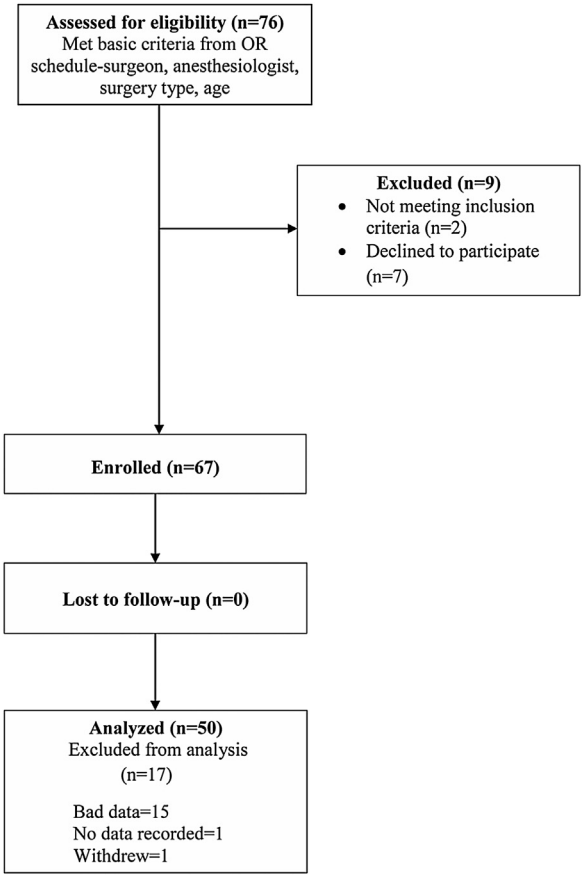

Figure 1 Strobe flow diagram for patient enrollment.

thesiology (ASA) status, surgical procedure and anesthetic technique were included.

Perioperative management at the study institution

Perioperative pain management at Hospital for Special Surgery followed standard of care procedures for patients undergoing THR and TKR.[10] These groups of patients typically receive Patient-Controlled Epidural Anesthesia (PCEA) for postoperative analgesia, with a combination of 0.06% bupivacaine and hydromorphone 10 mg.mL^{-1}, after combined spinal-epidural neuraxial anesthesia. Patients were assessed twice a day by the Acute Pain Service. Patients were typically started on oral analgesics as soon as they tolerate oral medications, and the PCEA was weaned as per the protocol in 24 hours in THR patients, and 36 hours in TKR patients. Postoperatively, THR/TKR patients are enrolled in multi-disciplinary clinical pathways. THR patients initiate physical therapy either on the afternoon of surgery or on the morning of POD1. The pathway for TKR patients includes continuous passive motion. Both pathways target twice a day ambulation on POD1 followed by progressively more activity. Physical Activity (PA) and the continuous passive motion were anticipated to be painful at POD1 and POD2.

SCA to assess SCR – equipment design

The SCA is a device from Med-Storm Innovation version 2005 that primarily measures changes in skin conductance in real time to assess pain in the patient. Measurements are performed using three self-adhesive non-invasive electrodes denoted C (Current), R (Reference) and M (Measurement) attached to the palmar or plantar side of the skin.[11,12] A skin conductance response is defined as a minimum followed by a maximum in conductance values microsiemens (μS). From the skin conductance response, SCR can be calculated in real-time and used for pain assessment, typically analyzed in a sliding 15 seconds window updated each second.[12]

The measurement unit uses the C and R electrodes in a feedback configuration to apply an exact and constant alternating voltage between the R and M electrodes. The return current from the M-electrode is recorded, as its value provides direct information on the skin conductance. The recorded alternating current signal is subjected to advanced filtering which removes noise and interference before the signal is sent on to the display computer.[11,12]

The system can measure conductance values in the range 1–200 μS, with a noise level below 0.002 μS. The measuring unit also has error detection that provides a warning for events caused by a loose electrode, external interference, or the use of electrocoagulation.[11,12] The threshold for SCR recordings in this study was 0.005 μS, according to the preset values of the monitor.

Electrodes used for the SCA

Electrodes containing AgCl are used and the measuring area under the M-electrode is critical, because the SCR reflects the number of sweat glands below the electrode. The density of sweat glands on the palmar and plantar surface of hand/foot is consistent,[1,13] so it is not critical where the electrodes are placed within these areas. The M-electrode is suited for the indices in the SCA.[11,12]

NRS to assess pain and anxiety

The NRS was used to assess pain and anxiety (0 = no pain or anxiety; 10 = worst possible pain or anxiety).[3,14,15]

Nausea assessment

Nausea was assessed by patients' self-report on their level of nausea on a 0–3 scale: 0 = no nausea; 1 = mild; 2 = moderate; 3 = severe. The research assistant also assessed the nausea with a ''yes'' or ''no'' outcome based on their observation.

Intellectual task assessment

The intellectual task was assessed based on patients' performance in subtracting 7 from 100 successively for 30 seconds.[16]

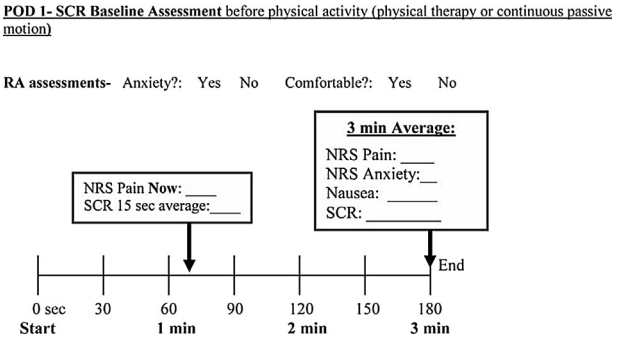

Figure 2 The procedure for when the Skin Conductance Responses (SCR), nausea, anxiety Numeric Rating Scale (NRS), and pain (NRS) were assessed before, during and/or after physical activity; physical therapy and continuous passive motion, as well as during intellectual task at Postoperative Day (POD) 1.

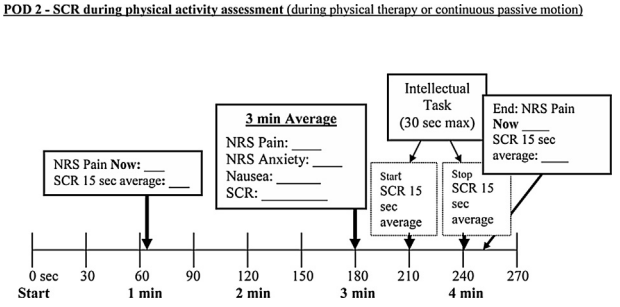

Figure 3 The procedure for when the Skin Conductance Responses (SCR), nausea, anxiety Numeric Rating Scale (NRS), and pain (NRS) were assessed before, during and/or after physical activity; physical therapy and continuous passive motion, as well as during intellectual task at Postoperative Day (POD) 2.

Study design

For both surgical patient groups, THR and TKR, baseline readings were measured for approximately 3 minutes on the morning of POD1 before PA (baseline). Additionally, readings were performed during PA lasting approximately 3 minutes both in POD1 and POD2, for pain, anxiety, nausea, and SCR. It was elected to have the readings during PA, as physical activity is expected to increase the pain postoperatively. Increased pain during PA may influence the anxiety, nausea and SCR postoperatively and thereby to help us to exclude those patients with moderate-severe pain. The patients with no pain–mild pain would be suitable[12] to study the emotional stressors in this group of patients in the absence of moderate-severe pain. A period of intellectual task was performed after PA lasting for 30 seconds to study how it influenced the SCR, during both Postoperative Day (POD) POD1 and POD2. The increases from start to end of the intellectual task according to the SCR (15 seconds) were assessed. Finally, momentary pain and SCR in real time (15 seconds) were studied at baseline, during and after PA on both POD1 (Fig. 2), and POD2 (Fig. 3).

The patients received epidural analgesia with creation of sympathetic block in the lower extremities, the SCA measurements were conducted on the palmar surface of the hand. Therefore, sensory dermatomal levels were tested in all patients to rule out the influence of sympathetic block created by epidural analgesia on the hand measurements of SCA. There have been publications indicating that the level of sympathetic block averaged two spinal segments higher than the level of somatic sensory analgesia to pinprick.[17,18]

Table 1 Patient demographics, American Society Anesthesiologist Physical Status Classification System (ASA), Body Mass Index (BMI), surgical procedure and anesthetic technique.

Characteristic	Total
Gender, M/F (%)	52/48
Age (mean ± SD)	64.1 ± 8.7
BMI, kg/m^2 (mean ± SD)	30 ± 6
Race, caucasian/other (%)	94/6
ASA (mean ± SD)	2.2 ± 0.5
Procedure (%)	
Total hip replacement	48
Total knee replacement	52
Anesthesia technique (%)	
General	0
Regional (combined spinal-epidural)	100

Statistics

Skin conductance activity (assessed by SCR) has shown statistical significant increase during painful events in several studies.[8,9,11,15,19–23] In these studies, the number of patients included to obtain statistically significant changes were between 20 and 75. Therefore, in this study we estimated that 50 patients would be appropriate to study how the SCR correlate with pain, anxiety, intellectual tasks and nausea. Sixty seven patients were included, 17 were excluded from analysis. The remaining 50 patients undergoing either Total Hip Replacement (THR) or Total Knee Replacement (TKR) procedures were enrolled. We performed an exploratory analysis of 50 patients.

To investigate potential differences between THR and TKR, the Mann Whitney U-test was used to compare the average levels of 180 seconds for pain, anxiety, nausea, and SCR at baseline, and during PA at POD1 and POD2. To study the differences from baseline to PA on POD1 and POD2 for the 180 seconds average values, Friedman's test for multiple comparisons was utilized. Skin Conductance Response (SCR) was analyzed by Friedman's test from the start (15 seconds) to end (15 seconds) of the intellectual task in POD1 and POD2 in both Total Knee Replacement (TKR) and Total Hip Replacement (THR) patients. Spearman's correlation analyses were used for the 180 seconds average values to determine the influence of anxiety on pain or SCR during PA on POD1 and POD2 for all patients. Spearman's correlation analyses were used for these 180 seconds average values to correlate SCR with nausea during PA on POD1 and POD2 for all patients, as well as for the momentary correlations between SCR and pain during and after the performances. Since this was an exploratory study, correction for multiple analyses was not justified and $p < 0.01$ was accepted as statistically significant. The statistics were performed with SPSS statistics 25.

Table 2 Skin Conductance Response (SCR), pain (Numeric Rating Scale – NRS) and anxiety (NRS), and nausea were compared from baseline to during Physical Activity (PA) at postoperative day (POD) POD1 and POD 2. Values are expressed as mean ± SD.

	Baseline (180 s)	POD1 during PA (180 s)	POD2 during PA (180 s)	*p*-value
SCR	0.13 ± 0.15	0.08 ± 0.12	0.11 ± 0.12	0.062
Pain (NRS)	2.0 ± 2.2	2.7 ± 2.4	2.9 ± 2.0	< 0.0001
Anxiety (NRS)	1.0 ± 2.2	0.92 ± 1.7	1.25 ± 2.2	0.990
Nausea	0.16 ± 0.51	0.20 ± 0.6	0.16 ± 0.51	0.607

Table 3 Skin Conductance Response (SCR) was compared from the start to end of the Intellectual Task (IT) at Postoperative Day (POD1 and POD2) in Total Knee Replacement (TKR) and Total Hip Replacement (THR) patients combined. Values are expressed as mean ± SD.

	Start IT (15 s)	End IT (15 s)	*p*-value
SCR, POD 1	0.15 ± 0.15	0.18 ± 0.17	0.189
SCR, POD 2	0.17 ± 0.17	0.22 ± 0.19	0.073

Results

Fifty patients were included in the study. A STROBE flowchart of the participants is presented in Figure 1, indicating the recruitment of individuals. Patient demographics are described for the different groups in Table 1.

There were no differences between THR and TKR in pain, anxiety, nausea, and SCR during PA (average values for 180 seconds). NRS increased with PA from baseline in both POD1 and POD2 (mean ± SD) 2.0 (2.2) to 2.7 (2.4), and 2.9 (2.0) ($p < 0.0001$) (average values for 180 seconds), which corresponds to mild pain (Table 2). SCR, anxiety, and nausea did not increase during PA (average values for 180 seconds) (Table 2). The SCR levels were 0.08 (0.12) and 0.11 (0.12) during PA (average values for 180 seconds), which corresponds to mild pain according to the SCA Index[9,10,24] (Table 2).

SCR did not increase significantly during intellectual task on POD1 and POD2 (Table 3). The mean SCR levels during intellectual task ended at 0.18 and 0.22 which corresponds to mild-moderate pain according to the SCA index (Table 3).

Anxiety versus pain correlated for PA on POD1 ($\rho = 0.51$, $p < 0.0001$), as opposed to anxiety versus SCR (average values for 180 seconds), which did not show a significant correlation (Table 4). Neither pain versus SCR, nor nausea versus SCR was found to correlate significantly (average values for 180 seconds) (Table 4).

When the relationship between momentary pain and SCR in real time (average value for 15 seconds) was investigated at baseline, and during and after PA, no significant correlations were found (Table 5).

Table 4 Correlations of anxiety, pain, nausea, and Skin Conductance Response (SCR) during Physical Activity (PA) on Postoperative Day (POD1 and POD2) in patients undergoing Total Knee Replacement (TKR) and Total Hip Replacement (THR). Anxiety levels were correlated with pain using Numeric Rating Scale (NRS) for both modalities. SCR was correlated with pain, anxiety, and nausea. The 95% Confidence Intervals are presented for statistically significant correlations, and are indicated with superscripts ([a,b]).

THR and TKR (n = 50) – average values (180 s) during PA	*ρ*-value	*p*-value
POD1		
Anxiety vs. Pain	0.51[a]	< 0.0001
Anxiety vs. SCR	0.26	0.065
Pain vs. SCR	0.27	0.118
Nausea vs. SCR	0.19	0.544
POD2		
Anxiety vs. Pain	0.32[b]	0.022
Anxiety vs. SCR	0.10	0.650
Pain vs. SCR	0.18	0.093
Nausea vs. SCR	0.18	0.320

[a]95% CI: 0.28–0.70; [b] 95% CI: 0.05–0.61; ρ-value, correlation coefficient.

Table 5 Mean ± SD values and correlations of momentary pain, Numeric Rating Scale (NRS) and Skin Conductance Responses (SCR) in real time (15 seconds analyzing window) during and after Physical Activity (PA) at Postoperative Day (POD1 and POD2) in patients undergoing Total Knee Replacement (TKR) and Total Hip Replacement (THR).

	Pain (NRS) (15 s)	SCR (15 s)	*ρ*-value	*p*-value
BASAL	2.1 ± 2.3	0.09 ± 0.11	0.19	0.19
POD1				
During PA	3.1 ± 2.4	0.06 ± 0.11	0.25	0.078
After PA	2.6 ± 2.3	0.08 ± 0.08	0.14	0.331
POD2				
During PA	3.2 ± 2.2	0.09 ± 0.10	-0.05	0.743
After PA	2.6 ± 2.1	0.10 ± 0.08	-0.14	0.321

p-value, correlation coefficient.

Discussion

Both NRS and SCR showed mild pain, and SCR did not correlate with NRS. SCR was not influenced by intellectual task performance. There were no correlations between SCR and anxiety, or between SCR and nausea. The NRS during physical activity showed mean values of 2.7–2.9, and the SCR showed a mean value of 0.08–0.11, both of which correspond to mild pain according to the SCA Index.[8,9,11] The mean SCR values during intellectual task performance, 0.18–0.22, were in the range of mild-moderate pain according to the SCA index which is based on SCR.[8,9,11] The intellectual task

performance was studied after PA, which was anticipated to be painful. There is possibility that the pain from PA might have extended into the period of the intellectual task measurement. There was a correlation between reported pain, and level of anxiety similar to previous studies.[4,15]

It has been shown in animal and clinical studies that acute pain causes an increase in skin sympathetic activity.[6–9,11,15,19–21] Various studies have been performed in adults and children by monitoring the SCR to assess pain levels.[6–9,11,15,19–21] Similar results were obtained for children and adults postoperatively with sensitivity to discover moderate-severe pain of 90% if a cut-off value of 0.20 SCR was used.[8,9,21] The specificity to discover moderate-severe pain was about 70% for adults, and 64% for children in postoperative patients, when a preset analyzing window of 15 seconds was used.[8,9,21] During anesthesia when a surgical stress score was used, the specificity increased to 86% to assess painful stimuli,[23] indicating that patients with a higher level of sedation have higher specificity to painful stimuli compared to patients with less sedation.

The SCR is evident within 1–2 seconds after stimulation.[11] As it is acetylcholine which acts on muscarinic receptors, one advantage of SCR over the hemodynamic parameters such as blood pressure and heart rate monitoring is that the SCR is not influenced by changes in peripheral blood flow, use of vasoactive medications such as epinephrine or beta-blockers, general hypoxia, respiratory rhythm or environmental temperature (18–42 °C).[25] Studies showed that SCR was a useful variable for objectively assessing acute postoperative pain[8,9,11,15,21] and pain assessment in patients in the ICU.[19,20] In addition to pain, there is evidence that SCR may be influenced by other factors inducing emotional stress such as anxiety, intellectual task performance,[26] and nausea. In children[21] and adult,[15] anxiety was not found to influence the SCR. If the SCR is to be used in the perioperative setting, it is important to examine how other emotional stressors besides pain influence the index. This study shows that intellectual task performance, nausea and anxiety do not influence the SCR postoperatively. A previous study[26] showed that intellectual task may influence SCR. In that study the intellectual task performance was longer in duration, and was not tested in the postoperative setting. The reported level of pain may be elevated by high anxiety levels.[4,15] This concept was confirmed in this study by observing a positive correlation between anxiety and reported pain. Pain-related anxiety is associated with over-predicting the intensity of a new pain experience.[27] One may speculate that a reduction of patients' anxiety levels will also reduce the level of reported pain.

The reason for selecting two different types of surgical patients was to have two different patient populations with relatively different postoperative pain levels. It has been our experience that, in general, TKR patients report higher pain levels, require more pain medications and need analgesia for a longer duration postoperatively, as compared to THR patients. Interestingly, both these patient groups reported similar pain (no pain-mild pain) levels, SCR, anxiety and nausea during measurements.

We used SCR measurement in the upper extremity while the patients received epidural analgesia postoperatively (after the spinal anesthetic wore off from combined spinal-epidural anesthesia) with use of low dose local anesthetic. There may be a theoretical concern that the lumbar neuraxial analgesia might have affected the SCR measurements in the hand. In another study, the SCR measurement in the hand was abolished when the patients received a spinal block.[28] In our study, measurements were obtained during the phase of low-dose epidural analgesia after the dense spinal anesthesia wore off in the POD1. The spread of epidural anesthesia is within several dermatomes as compared to spinal anesthesia. Therefore, we expect the medications to spread to several dermatomes proximal and distal to level of epidural catheter placement in the lower lumbar levels (L3–S1 range in our study). This is in contrast to spinal anesthesia that may have a wider range of dermatomal spread as the medication is being introduced to cerebrospinal fluid. We also note from the same study that it is significantly more difficult to block sympathetic responses than to block the sensory and motor responses in neuraxial anesthesia. There is only partial abolition of the SCR in the foot after a spinal block and sympathetic activity returned prior to observation of regression of analgesia or motor blockade. In addition, the interval of sympathetic blockade was much shorter than analgesia and motor blockade.[28] Another pilot study demonstrated that the SCR is maintained at dermatome levels significantly below the blocked levels during dense spinal anesthesia.[29] In our study, sensory dermatomal level was tested in all patients bilaterally by pinprick and cold application to determine the extent of cranial spread of the sensory block and the highest level of sensory level was documented as T8. The sympathetic level is generally two to three dermatome levels higher than the sensory level. Therefore, although there is a possibility that the measurements of SCR in the hand might have been abolished, we believe that in our study, this effect was negligible.

In this study, the physical activity might have increased the pain levels, but reported pain levels were still low due to adequate postoperative analgesia. Because the pain levels were mild and lower than anticipated the sensitivity and specificity for moderate and severe pain were not calculated.

Some limitations were present in the current investigation. We were not able to show any correlation between the SCR and postoperative pain scores when the pain levels were reported to be mild. There have been multiple studies which reported correlations between pain scores and the SCR for moderate and severe pain. Our results might have been different if the patients in the present study had reported a higher level of pain. This study is an exploratory study, and the results should be interpreted accordingly. Other limitation is that this study did not look into the amount of analgesia given to the different patient groups, which may have explained why the reported pain was similar in both groups of patients. The patients had PCEA, which might have led to variations in levels of analgesia, and thereby change the responses to the painful stimulus.

Conclusions

There was no correlation found between assessment of pain by using SCR and NRS with the cut-off values used in this exploratory pilot study. This pilot study suggests that when the pain is well-controlled in the early postoperative period,

SCR monitoring may not be influenced by other emotional stressors such as intellectual task performance, anxiety or nausea. Further studies are required to determine whether SCR may be a viable physiological monitor for the assessment of acute pain postoperatively as well as to determine the cut-off values that will best predict the sensitivity and specificity.

Author's contribution

Conceptualization: Semih Gungor, Hanne Storm. Data curation: James J.Bae, Valeria Rotundo. Formal analysis: Semih Gungor, Hanne Storm, Paul Christos. Methodology: Semih Gungor, Hanne Storm, Paul Christos. Project administration: Semih Gungor. Supervision: Semih Gungor. Validation: Semih Gungor, Hanne Storm, Paul Christos. Writing — review & editing: Semih Gungor, Hanne Storm, James J.Bae, Valeria Rotundo, Paul Christos.

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Conflicts of interest

Hanne Storm has a potential competing interest as a part owner, CEO and share-holder in Med-Storm Innovation AS, and has contributed to the development of the skin conductance monitor used in the study. Med-Storm Innovation AS has patents on the skin conductance equipment used in this study for measuring pain and sedation level. Med-Storm Innovation provided the skin conductance device, (MED-STORM AS 2005) for this study. The other authors declare no conflicts of interest.

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