The Effect of Spinal Cord Stimulation on Thermal Forward Looking InfraRed Imaging in Complex Regional Pain Syndrome

FUNDER: Anesthesiology Department

PROTOCOL NO.: 2022-2480

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PROTOCOL SYNOPSIS

Protocol Title:	The Effect of Spinal Cord Stimulation on Thermal Forward Looking InfraRed Imaging in Complex Regional Pain Syndrome
Protocol Number:	2022-2480
Protocol Date:	2/22/2023
Sponsor:	Anesthesiology Department, Hospital for Special Surgery
Principal Investigator:	Semih Gungor, MD
Products:	N/A
Objective:	This research proposal aims to investigate the potential use of Forward Looking Infrared (FLIR) imaging to monitor whether the sympatholytic effect is enhanced by using spinal cord stimulation in chronic regional pain syndrome patients.
Study Design:	Observational, prospective cohort
Enrollment:	10
Subject Criteria:	Inclusion Criteria: • The patient is between 18 and 85 years old • Providing CRPS diagnostic criteria by using the Budapest Clinical Diagnostic Criteria. • The patient has had pain and other symptoms for more than 3 months • Not responding to conventional medical treatments and multidisciplinary approach • High NRS detection in pain assessment despite appropriate treatment (NRS= and > 6/10). • Pain causing a limitation in the patient's functional capacity despite appropriate treatment.
	Exclusion Criteria: • Patients with suspected disc herniation, spinal stenosis, myelopathy, and suspected radiculopathy in detailed examinations and examinations (MRI, CT). • Systemic or local infection • Coagulation disorders • History of allergy to contrast material. • Malignancy • Pregnancy • Uncontrollable medical and psychiatric condition • The patients diagnosed with dysautonomia, sympathetic dysfunction other than CRPS (such as Raynaud disease or Buerger disease), sweating disorders other than CRPS (such as acquired idiopathic generalized anhidrosis), and patients.
Study Duration:	• 1 year
Data Collection:	•

Outcome Parameters:	**Primary Outcome:** Improvement in temperature difference Primary Outcome Definition: 30% or more improvement in temperature difference in the affected limb by FLIR camera in at least 50% of CRPS patients at 48 hours after spinal cord stimulation. Associated Variable(s): -Temperature Difference - Time (48 hours)
	Secondary Outcomes: 1) Pain (NRS) Definition: Quantitative measures (delta thermal camera value) are expected to provide a 50% or higher correlation to NRS values (the delta pain NRS value). (The developed quantitative measurement will be compared with the currently used NRS values at postoperative follow-up (1-2 weeks) time points after completion of the SCS.) Associated Variable(s): The delta thermal camera value and the delta NRS value. 2) CRPS Severity Score (CSS) Definition: Quantitative measures (delta thermal camera value) are expected to provide a 50% or higher correlation to CSS values (the delta pain CSS value). (The developed quantitative measurement will be compared with the currently used CSS values at postoperative follow-up (1-2 weeks) time points after completion of the SCS.) Associated Variable(s): The delta thermal camera value and the delta CSS value. 3) Health Related Quality of Life (HRQoL) Definition: Quantitative measures (delta thermal camera value) are expected to provide a 50% or higher correlation to HRQoL values (the delta pain QoL value). (The developed quantitative measurement will be compared with the currently used HRQoL values at postoperative follow-up (1-2 weeks) timepoints after completion of the SCS.) Associated Variable(s): The delta thermal camera value and the delta HRQoL value. 4) Neuropathic pain score (PainDetect-PD) Definition: Quantitative measures (delta thermal camera value) are expected to provide a 50% or higher correlation to PD values (delta painPD value). (The developed quantitative measurement will be compared with the currently used PD values at postoperative follow-up (1-2 weeks) time points after completion of the SCS.) Associated Variable(s): The delta thermal camera value and the delta PD value
Data Evaluation:	
Statistical Analysis:	1. **Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.):** We will rely on students t-test when comparing

	pairs of groups and ANOVA when comparing multiple groups; regression will be used to assess strength of relationship between NRS and objective diffusion metrics. 2. **Interim analysis planned? No** 3. **Alpha level:** 0.05 4. **Beta or power level:** target beta level 0.2 or less 5. **Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):** The impact of thermal camera-based quantification of treatment effectiveness will be assessed on the affected extremity. The values before the block will be compared with the values after the block to explore the validity and the reliability of the method. In particular, we will perform power analyses where we consider the Null hypotheses of the form: “The proposed method does not provide better results than the existing result” or, equivalently, “accuracy_mean(proposed method) not greater than accuracy_mean(old method)”? 6. **Number of groups being compared (use 1 for paired analysis within the same subjects):** 1 (paired analysis within the same subjects) 7. **Effect size or change expected between groups:** N/A (Pilot study) 8. **Resulting number per group: 10 patients** 9. **Total sample size required:** No similar study available in the literature to calculate the sample size required for this proposed study, so we will take the pilot study approach and collect sample data in 10 procedures. We will calculate the means and standard deviations for the two distributions.

1.0 INTRODUCTION

The primary mechanism of pain relief by SCS therapy can be explained by the gate control theory [1]. SCS sends electrical stimulation to the dorsal column to mask the pain sensation due to the concomitant blockade of small diameter C and A-delta nerve fibers [2]. SCS has been used in treating neuropathic pain in the limbs with good outcomes, including in patients with CRPS in refractory cases [3,4].

The literature shows the physiological activation of cutaneous vasoconstrictor neurons in CRPS patients with sympathetically maintained pain, thereby enhancing spontaneous pain and hyperalgesia [5]. According to our knowledge, SCS can relieve ischemic pain and enhance peripheral circulation [6,7,8]. SCS can increase cutaneous blood flow in the lower extremities by peripheral vasodilatation. The possible mechanism can be a transitory inhibition of sympathetic vasoconstriction by sympatholytic effects [8]. There is also information that the dorsal column can activate stimulation afferent fibers in the dorsal roots that cause the peripheral release of CGRP, which produces cutaneous vasodilation [6]. Therefore, the clinical expectation of SCS treatment in CRPS patients is increasing temperature in the affected limb. In a case report about a CRPS patient, the treatment outcomes showed that SCS could increase microcirculation in CRPS patients with a thermogram study [9].

The 17 signs and symptoms derived from 'the Budapest Criteria' [10] are the components of 'the CRPS Severity Score' (CSS). The resulting CSS ranged potentially from 0 to 17, with higher scores indicating greater CRPS severity. It is indicated that higher CSS could be associated with significantly higher clinical pain intensity, distress, and functional impairments [11]. In addition, the higher CSS score can point to greater bilateral temperature asymmetry and thermal perception abnormalities [11].

CRPS may have a significant impact on patients' life. The information about health-related quality of life (HRQoL) in CRPS patients correlates with levels of disability [12].

The quantitative measurements of circulation with delta thermal camera value are expected to correlate with patients' NRS, CSS, and HRQoL.

References:
1. Melzack R, Wall PD. Pain mechanisms: A new theory. Science1965;150(3699):971–9.

2. Harden RN, McCabe CS, Goebel A, Massey M, Suvar T, Grieve S, Bruehl S.Complex Regional Pain Syndrome: Practical Diagnostic and Treatment Guidelines,5th Edition. Pain Med. 2022 Jun 10;23(Suppl 1):S1-S53. doi: 10.1093/pm/pnac046.PMID: 35687369; PMCID: PMC9186375.

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12. van Velzen, Gijsbrecht A.J.a,b,*; Perez, Roberto S.G.M.b,c,d; van Gestel,Miriam A.b,e; Huygen, Frank J.P.M.b,f; van Kleef, Maartenb,g; van Eijs, Frankb,h;Dahan, Albertb,i; van Hilten, Jacobus J.a,b; Marinus, Johana,b. Health-relatedquality of life in 975 patients with complex regional pain syndrome type 1. Pain155(3):p 629-634, March 2014. | DOI: 10.1016/j.pain.2013.12.017

2.0 PRODUCT DESCRIPTION

FLIR camera is non-invasive (no patient contact) device without any known harmful effects to living cells and is accepted as “FDA exempt” status.

3.0 OBJECTIVE OF CLINICAL STUDY

This research proposal aims to investigate the potential use of Forward Looking Infrared (FLIR) imaging to monitor whether the sympatholytic effect is enhanced by using spinal cord stimulation in chronic regional pain syndrome patients.

4.0 STUDY HYPOTHESES

Hypothesis 1: When comparing the FLIR images taken before and after the SCS trial lead placement, there will be significant differences in circulation and perfusion (delta thermal camera value) in the affected limb at 48 hours post-procedure.

Hypothesis 2: When a significant difference in perfusion of the extremity after the SCS is observed, this change (delta thermal camera value) will be correlated with the patient outcome measures (delta value of each outcome measure); this will enable quantification of the correlation between the improvement of perfusion with SCS in CRPS patients.

5.0 STUDY DESIGN

5.1 Study Duration

1 year from the start of enrollment

5.2 Endpoints

5.2.1 Primary Endpoint

Improvement in temperature difference

Primary Outcome Definition: 30% or more improvement in temperature difference in the affected limb by FLIR camera in at least 50% of CRPS patients at 48 hours after spinal cord stimulation.
Associated Variable(s):
-Temperature Difference
-Time (48 hours)

5.2.2 Secondary Endpoints

1) Numerical Rating Scale Pain (NRS)
Definition: Quantitative measures (delta thermal camera value) are expected to provide a 50% or higher correlation to NRS values (the delta pain NRS value). (The developed quantitative measurement will be compared with the currently used NRS values at postoperative follow-up (1-2 weeks) time points after completion of the SCS.)

Associated Variable(s): The delta thermal camera value and the delta NRS value.

2) CRPS Severity Score (CSS)
Definition: Quantitative measures (delta thermal camera value) are expected to provide a 50% or higher correlation to CSS values (the delta pain CSS value). (The developed quantitative measurement will be compared with the currently used CSS values at postoperative follow-up (1-2 weeks) time points after completion of the SCS.)

Associated Variable(s): The delta thermal camera value and the delta CSS value.

3) Health Related Quality of Life (HRQoL)
Definition: Quantitative measures (delta thermal camera value) are expected to provide a 50% or higher correlation to HRQoL values (the delta pain QoL value). (The developed quantitative measurement will be compared with the currently used HRQoL values at postoperative follow-up (1-2 weeks) timepoints after completion of the SCS.)

Associated Variable(s): The delta thermal camera value and the delta HRQoL value.

4) Neuropathic pain score (PainDetect-PD)

Definition: Quantitative measures (delta thermal camera value) are expected to provide a 50% or higher correlation to PD values (delta painPD value). (The developed quantitative measurement will be compared with the currently used PD values at postoperative follow-up (1-2 weeks) time points after completion of the SCS.)

Associated Variable(s): The delta thermal camera value and the delta PD value.

5.3 Study Sites

Hospital for Special Surgery (Main Hospital)
535 E 70th St
New York, NY 10021

6.0 STUDY POPULATION

6.1 Number of Subjects

A total of 10 participants will be enrolled.

6.2 Inclusion Criteria

Subjects of either gender will be included if they:

- The patient is between 18 and 85 years old.
- Providing CRPS diagnostic criteria by using the Budapest Clinical Diagnostic Criteria.
- The patient has had pain and other symptoms for more than 3 months.
- Not responding to conventional medical treatments and multidisciplinary approach
- High NRS detection in pain assessment despite appropriate treatment (NRS= and > 6/10).
- Pain causing a limitation in the patient's functional capacity despite appropriate treatment.

6.3 Exclusion Criteria

Subjects will be excluded from the study if they:

- Patients with suspected disc herniation, spinal stenosis, myelopathy, and suspected radiculopathy in detailed examinations and examinations (MRI, CT).
- Systemic or local infection
- Coagulation disorders
- History of allergy to contrast material.
- Malignancy
- Pregnancy
- Uncontrollable medical and psychiatric condition
- The patients diagnosed with dysautonomia, sympathetic dysfunction other than CRPS (such as Raynaud disease or Buerger disease), sweating disorders other than CRPS (such as acquired idiopathic generalized anhidrosis), and patients.

7.0 PROCEDURES

7.1 Surgical Procedure

Patients undergoing a surgery that requires a spinal cord stimulation.

7.2 Imaging Procedure

FLIR Camera Measurements:

1. We will use a FLIR T420 or T62101 camera with 320*240 resolution.
2. Each image will be taken perpendicularly with a 1-inch space from all four sides.
3. The feet will be separated from the background with the help of a Myler blanket placed in the background.
4. The camera will be normalized to the temperate range at 15°C minimum and40°C maximum.
5. The images will be stored as radiometric JPEG.
6. Once the images are moved to a computer, we will apply background removal.
7. We will then create a temperature histogram with a temperature bin resolution of0.1°C
8. The before and after histograms (IB, IA) will be compared to determine which one implies higher temperature distributions.
9. Those with an improvement of 30% or more will be classified as having a successful spinal cord stimulation.

7.3 Data Collection

The following data will be collected:

Pre-operative/Baseline

- basic demographic data
- patient weight & height, BMI
- Numerical Rating Scale (NRS) Pain
- CRPS Severity Score (CSS)
- Quality of Life Score (SF-36)
- Neuropathic Pain Score (painDETECT)

Surgical procedure

- FLIR image of the affected lower extremity via the standard technique

Post-operative

- Numerical Rating Scale (NRS) Pain
- Outcome measures for function, QoL, and neuropathic pain at 48 hours
- FLIR image of the affected lower extremity via standard technique at 48 hours

Follow-up visits (1 week - 2 weeks)

- Numerical Rating Scale (NRS) Pain
- Outcome measures for function, QoL, and neuropathic pain
- FLIR image of the affected lower extremity via standard technique

8.0 STATISTICAL ANALYSIS

1. **Proposed analysis (e.g., student's t-test, ANOVA, chi-square, regression, etc.):** We will rely on students t-test when comparing pairs of groups and ANOVA when comparing multiple groups; regression will be used to assess strength of relationship between NRS and objective diffusion metrics.
2. **Interim analysis planned? No**
3. **Alpha level:** 0.05
4. **Beta or power level:** target beta level 0.2 or less
5. **Primary outcome variable estimate (mean +/- s.d. for continuous outcome, frequency/percentage for categorical variable):**
   The impact of thermal camera based quantification of treatment effectiveness will be assessed on the affected extremity. The values before the block will be compared with the values after the block to explore the validity and the reliability of the method. In particular, we will perform power analyses where we consider the Null hypotheses of the form: "The proposed method does not provide better results than the existing result" or, equivalently, "accuracy_mean(proposed method) not greater than accuracy_mean(old method)"?
6. **Number of groups being compared (use 1 for paired analysis within the same subjects):** 1 (paired analysis within the same subjects)
7. **Effect size or change expected between groups:** N/A (Pilot study)
8. **Resulting number per group: 10 patients**
9. **Total sample size required:** No similar study available in the literature to calculate the sample size required for this proposed study, so we will take the pilot study approach and collect sample data in 10 procedures. We will calculate the means and standard deviations for the two distributions.

9.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report. Definitions for Adverse Event (AE) used in this study are listed below and are based on FDA and international guidelines:

10.0 REFERENCES

1. Melzack R, Wall PD. Pain mechanisms: A new theory. Science 1965;150(3699):971–9.
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