Severity of Autonomic Dysfunction in Patients with Spinal Cord Injury: Evaluation and Validation of the Ewing Criteria for Autonomic Nervous System Assessment in Spinal Cord Injury

Included Documents:

Study Protocol, Statistical Analysis Plan, and Informed Consent Form

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PART 1: STUDY PROTOCOL

1. Introduction and Rationale

Spinal cord injury (SCI) severely disrupts autonomic nervous system (ANS) pathways, causing extensive cardiovascular, thermoregulatory, visceral, and immunological dysfunctions. The loss of supraspinal control leads to life-threatening complications such as autonomic dysreflexia (AD) and orthostatic hypotension (OH). Although neurophysiological autonomic assessments are widely utilized in other conditions, a validated protocol for SCI patients is currently lacking. This study aims to validate the Ewing Battery—comprising standardized, non-invasive cardiovascular tests—for the detection and classification of dysautonomia in individuals with SCI.

2. Study Objectives

Primary Objective: To validate the standardized Ewing criteria as a reliable diagnostic methodology for evaluating cardiovascular autonomic dysfunction in patients suffering from spinal cord injury.

Secondary Objectives:

- Define tailored diagnostic cut-off points for the Ewing tests specifically for the SCI population, stratified by anatomical injury level and neurological completeness.
- Compare objective autonomic parameters between SCI patients with lesions located at or above T6 versus below T6.
- Correlate initial Ewing test metrics with the objective incidence of clinical autonomic complications (AD, OH, syncope, and all-cause hospitalizations) over a 12-month prospective follow-up.

3. Eligibility Criteria

Inclusion Criteria:

- **Healthy Control Group:** Asymptomatic adults aged 18 to 60 years, with no prior medical conditions or comorbidities.
- **Spinal Cord Injury Group:** Adults aged 18 to 60 years presenting with a chronic traumatic or non-traumatic spinal cord injury (duration ≥ 12 months); applicable to any neurological level and ASIA Impairment Scale (AIS) grades A through D.

Exclusion Criteria:

- Concurrent use of medications that disrupt autonomic parameters (e.g., potent anticholinergics, non-selective beta-blockers, acetylcholinesterase inhibitors, antiarrhythmics).
- Coexisting diagnosis of diabetes mellitus presenting with established autonomic neuropathy.
- Concomitant severe chronic obstructive pulmonary disease (COPD) or uncontrolled asthma.
- Diagnosed alpha-synucleinopathies or related primary neurodegenerative disorders.
- Active atrial fibrillation, hemodynamically significant cardiac arrhythmias, or presence of an implanted artificial pacemaker or implantable cardioverter-defibrillator (ICD).

4. Study Procedures

Clinical assessments will be conducted in a quiet room maintained at a constant temperature (22–24°C). Participants will observe a light 3-hour fast. The standardized Ewing battery includes:

1. **Deep Breathing Test:** Heart rate variation mapped during deep breathing at a fixed rate of 6 cycles per minute to calculate the Expiratory/Inspiratory (E/I) ratio.
2. **Valsalva Maneuver:** The participant exhales forcefully against a resistance column, maintaining an intrathoracic pressure of 40 mmHg for 15 seconds, to calculate the Valsalva Ratio and assess blood pressure recovery.
3. **Orthostatic Stress (Heart Rate):** Postural transition from a supine to an upright position using a tilt table to calculate the 30:15 ratio.
4. **Orthostatic Stress (Blood Pressure):** Continuous beat-to-beat monitoring during the postural transition to evaluate maximal decreases in systolic and diastolic blood pressure.

Safety Protocol: A trained physician will be present continuously. Sublingual nitrates will be available at the bedside. Tests will be immediately terminated if systolic blood pressure exceeds 180 mmHg, increases 20 mmHg or more above baseline, or if the participant displays early clinical signs of autonomic dysreflexia.

PART 2: STATISTICAL ANALYSIS PLAN (SAP)

1. Sample Size and Power Calculation

The total required sample size is 46 participants (23 in the SCI cohort and 23 in the healthy control cohort). This calculation is based on achieving an 80% statistical power at a 5% significance level to detect meaningful differences in autonomic test alterations, anticipating a 73.3% alteration prevalence in the SCI group versus 23.3% in healthy individuals. Subgroup analyses are powered to detect large physiological effect sizes (Cohen's d > 0.8).

2. Endpoints

Primary Endpoints: Overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the classical Ewing severity categories (Normal, Borderline, Defined, Severe).

Secondary Endpoints: Optimized diagnostic cut-off points calculated via the Youden Index, stratified by anatomical injury level. Additionally, cumulative incidence and relative risk of clinical autonomic events (AD, OH, syncope, unplanned hospitalizations) over the 12-month follow-up period.

3. Statistical Methods

- **Descriptive Statistics:** Continuous variables will be summarized using means with standard deviations or medians with interquartile ranges, following normality distribution testing. Categorical variables will be expressed as absolute frequencies and percentages.
- **Diagnostic Accuracy Validation:** Receiver Operating Characteristic (ROC) curves will be used to optimize SCI-specific diagnostic thresholds. Procedural stability and reliability will be evaluated using the Intraclass Correlation Coefficient (ICC) and Bland-Altman limits of agreement plots.
- **Prospective Longitudinal Analysis:** Clinical event distributions over time will be analyzed using Kaplan-Meier survival curves, estimating the exact time elapsed until a participant experiences their first adverse event. Between-group survival differences will be evaluated via the log-rank test. Adjusted Multivariate Cox Proportional Hazards Regression models will be constructed to calculate hazard ratios for clinical events, adjusting for baseline covariates (e.g., age, injury level).

- **Significance Level:** All statistical tests will be interpreted with a predefined two-tailed alpha level of 0.05.

PART 3: INFORMED CONSENT FORM (ICF)

Research Data

Study Title: Severity of Autonomic Dysfunction in Patients with Spinal Cord Injury: Evaluation and Validation of the Ewing Criteria for Autonomic Nervous System Assessment in Spinal Cord Injury
Principal Investigator: Dr. André Tadeu Sugawara
Institution: Institute of Physical Medicine and Rehabilitation, Hospital das Clínicas, Faculty of Medicine, University of São Paulo (IMREA-HCFMUSP)

Participation

You are being invited to participate in the research study mentioned above. The text below provides all the necessary information about what we intend to perform. Your collaboration is highly important to us; however, if you choose to withdraw at any time, it will not cause you any issues. Your participation is completely voluntary. Before deciding, please read and understand the entire content.

Study Objectives and Procedures

The primary objective of this study is to validate the Ewing Battery as a reliable method for detecting dysautonomia in individuals with Spinal Cord Injury (SCI). If you agree to participate, you will undergo:

- **Cardiovascular Autonomic Testing:** Non-invasive cardiovascular stress tests to evaluate your autonomic nervous system. Tests will be performed in a temperature-controlled environment with continuous monitoring. The tests include heart rate variation during deep breathing, the Valsalva maneuver, and heart rate/blood pressure responses to postural changes using a specialized tilt table.
- **Longitudinal Follow-up:** You will be followed for 12 months via periodic telephone contacts to record the occurrence of clinical events (such as symptomatic orthostatic hypotension, autonomic dysreflexia, syncope, and hospitalizations).

Risks and Safety Mitigation

The physical risks associated with this study are minimal and limited to potential discomforts during the autonomic tests (such as temporary lightheadedness, mild headaches, or transient blood

pressure elevations). A trained clinical team and a physician will be present throughout the entire procedure. Emergency medication (sublingual nitrates) will be immediately available at the bedside, and testing will be stopped instantly if warning signs of autonomic dysreflexia emerge.

Confidentiality and Privacy

All information provided will be treated with absolute secrecy and confidentiality, used exclusively for scientific purposes. Your participation is voluntary, and you reserve the right to seek legal indemnity for any damages resulting from this research.

Participant Statement

I have been sufficiently informed about the study. I have discussed the information regarding my decision to participate. The objectives, procedures, potential discomforts, risks, and guarantees are clear to me. I voluntarily agree to participate in this study.

Participant Name (Printed) - [DE-IDENTIFIED FOR SUBMISSION]

Participant / Legal Representative Signature - [DE-IDENTIFIED FOR SUBMISSION]

Date - [DE-IDENTIFIED]

Investigator Signature