Protocol Title:

Comparison of Timing of Initiation on the Efficacy of Gabapentin in Treating Neuropathic Pain in Spinal Cord Injury (SCI).
2/4/20

ClinicalTrials.gov Identifier: NCT04256603

Introduction:

Neuropathic pain is a common complaint in those with spinal cord injury (SCI) that has a significant negative effect on quality of life. This makes the treatment of neuropathic pain a priority in the SCI population. Efficacy of various treatments, however, remains controversial. There is evidence to support that gabapentin and pregabalin have some benefit in reducing neuropathic pain (1). Other positive effects of gabapentin on those with SCI have also been demonstrated. However, there has not been a study on the influence of timing of initiation of gabapentin on the efficacy of using it to treat neuropathic pain in the SCI population. Such a finding could change the standard of care in treatment of acute SCI.

The pooled prevalence of neuropathic pain post spinal cord injury is 53% (2). Not only common, neuropathic pain is pervasive, affecting aspects of patients' lives including sleep, physical function, and mood that in turn impact their activities— work and recreational alike (3). Thus, neuropathic pain management contributes to quality of life for a majority of people with SCI.

Although a high priority, the treatment of neuropathic pain in SCI remains notoriously difficult (4). Treatments options may be divided into pharmacologic and non-pharmacologic. Pharmacologic agents studied include amitriptyline, gabapentin, pregabalin, opiates, lidocaine, ketamine, valproate, lamotrigine, levetiracetam and carbamazepine; the most studied of which are amitriptyline, gabapentin, and pregabalin (5).

Gabapentin's potential is not limited to neuropathic pain management, making it a particularly compelling treatment option in the population with acute SCI. Gabapentin leads to improvement in total motor scores (6-9), reduced spasticity, reduced autonomic dysreflexia, and improved mood (8, 9). Animal models suggest it may be neuroprotective in the acute phase of injury (10). In those who undergo spine surgery, regardless of presence of SCI, gabapentin given perioperatively leads to reduced opiate use and decreased pain in post-operative period (11). Additionally, when compared to narcotic alternatives, gabapentin has minimal side effects.

Neuropathic pain in SCI is common, impactful, and difficult to treat. Gabapentin is effective in the management of symptoms and concerns related to SCI including motor recovery, spasticity, and mood among others. This makes gabapentin an important pharmacologic intervention, which compels providers to define treatment guidelines related to its use. One aspect of which should relate to the timing of initiation of therapy. The goal of this study is to determine whether early initiation of treatment with gabapentin will decrease average pain scores and opiate use when comparted to late initiation of treatment with gabapentin in the population with acute SCI. Gabapentin, although used commonly, is not started in all patients with acute SCI but is often started at the onset of neuropathic pain. If gabapentin is found to be more effective when initiated early, it would be reasonable to start gabapentin immediately following acute SCI in all patients in whom it is not otherwise contraindicated.

1. Objectives

- Primary

  To determine if the time from injury influences the prevalence of neuropathic pain in acute SCI

  To determine if the use of gabapentin in the early acute period influences the prevalence of neuropathic pain in patients with acute SCI

  To compare the efficacy of acute verses subacute initiation of gabapentin in treating neuropathic pain in SCI

- Secondary

  To compare the overall pain scores

  To determine the prevalence of neuropathic pain in those with SCI at admission and discharge to the inpatient rehabilitation hospital

  To compare the use of opiates

  To compare the average daily change in Functional Independence Measure (FIM)

  To compare the change in total motor score on the ASIA impairment scale

  To identify side effects of treatment with gabapentin and their frequency

2. Endpoints

Primary

- Presence of neuropathic pain at time of enrollment and again around time of discharge (Douleur Neuropathique 4, DN4)
- Neuropathic pain level (Neuropathic Pain Scale, NPS) at time of enrollment and again around time of discharge

Secondary

- Average pain level recorded in nursing flowsheet (Numeric Pain Rating Scale, NPRS)
- Weekly total use of opiates (total morphine milligram equivalents, MME)
- Change in FIM during rehabilitation
- Change in total motor score on the ASIA impairment scale during entire rehabilitation course
- Side effects attributed directly to gabapentin in physician documentation and whether or not gabapentin was stopped due to these side effects

3. Design

- Prospective, observational, cohort, single center study
- The study will enroll subjects with acute spinal cord injury who are admitted to acute inpatient rehabilitation at MetroHealth Rehabilitation Institute (MRI).

- After enrollment, subjects will be followed through the end of their acute rehabilitation stay including any interruption in rehabilitation for which they require ED evaluation and/or acute hospital readmission so long as they return to MRI.
- Around the time of enrollment, subjects will be asked to complete the DN4 questionnaire and the NPS.
- Around the time of discharge, subjects will be asked to complete a second DN4 questionnaire and the NPS.
- The remainder of the data collection will be through review of the patient's electronic medical record (EMR).
- Patients will be divided into those who first received gabapentin during their acute inpatient hospitalization, prior to admission to acute rehabilitation, and those who did not. Additionally, the timing of gabapentin initiation will also be recorded.

4. Subject selection

- Study population
  Subjects are patients who suffered acute spinal cord injury for which they are admitted to acute inpatient rehabilitation at MRI.
- Inclusion criteria
  Subjects who meet all the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion is met
    1. Clinical diagnosis of acute spinal cord injury
    2. Admission to MRI for acute inpatient rehabilitation
- Exclusion criteria
  Subjects who meet one or more of the following criteria will be excluded from this clinical study.
    1. Unable to communicate verbally or by writing, unable to follow basic instructions, or unable to answer questions regarding their symptoms

5. Subject Accountability

- Point of enrollment
  The point of enrollment is the time at which time a subject signs and dates the valid, IRB approved informed consent form. No study-related procedure or assessments can take place until the informed consent form is signed.
- Withdrawal
  All subjects enrolled to the study (including withdrawal or lost to follow-up) shall be accounted for and documented.
  Reasons for withdrawal include:
    1. Physician discretion
    2. Subject choice
    3. Lost to follow up
    4. Death

Subjects may withdraw from the study at any time, with or without reason without prejudice to further treatment.

6. Study methods

- Pre-screening
  To determine eligibility for enrollment into the study, the inclusion and exclusion criteria must be assessed.
- Informed consent
  After a patient has been identified as a potential candidate, based on meeting all inclusion and no exclusion criteria, written Informed Consent must be obtained by asking patients to read and review the valid IRB-approved Informed Consent. The informed consent process will abide by the MetroHealth Medical Center IRB process.
- Initial Visit
  The initial visit will occur at or within 7 days of the time of enrollment and admission to rehabilitation
  - Visit Type: Visit to patient while they are admitted to hospital
    - Admission DN4 and NPS
- Final Visit
  The final visit will occur at or within 7 days of the time of discharge from MRI
  - Visit Type: Visit to patient while they are admitted to hospital
    - Discharge DN4 and NPS
- Additional data collection: As outlined in Figure 2
  The data collection will be completed via review of the EMR of each subject, and will include the following:
  - Demographics
    - Age
    - Sex
    - Race
    - History of drug use
    - History of smoking
  - Home pain medications prior to SCI injury
  - Date of injury
  - ASIA impairment scores (AIS; 1st documented AIS, rehabilitation admission AIS, and rehabilitation discharge AIS)
  - Operative vs nonoperative management of SCI
  - Length of stay in rehabilitation
  - Rehabilitation admission and discharge FIM scores
  - Rehabilitation admission and discharge total motor scores (TMS) as recorded on AIS
  - Pain scores (NPRS)
    - Average score per week from injury as documented in EMR
  - Opiate use
    - Total weekly MME per week from injury

- Side effects
  - Record side effects attributed to gabapentin by treating physician
  - Record if therapy was stopped and why (ineffective, no longer required, adverse reaction)

7. Statistical Analysis Plan

   Subject demographics will be summarized by typical descriptive statistics to compare means or medians and measures of variability

   The relationship between the presence of neuropathic pain and: 1) the time from injury; 2) the timing of gabapentin initiation will be evaluated by building logistic regression models with dichotomous neuropathic pain (measured by DN4) as the dependent variable and time as the independent variable. Potential confounding variables will be added to the model if independently associated with the outcome of interest or based on theoretical grounds.

   The efficacy of gabapentin by timing of initiation will be analyzed with a regression model with change in pain on the Neuropathic Pain Scale from admission to discharge with timing of gabapentin initiation as the independent variable. Potential confounding variables will be added to the model if independently associated with the outcome of interest or based on theoretical grounds.

8. Data analysis

   - All enrolled subjects will be eligible for evaluation.

9. Data Safety/ Monitoring

   The PI and co-investigators will monitor the progress of the research study, including assessments of data quality, participant recruitment, accrual and retention, subject's confidentiality, any adverse event(s), and external factors or relevant information that might have an impact on the safety or ethics of the study.

   After recruitment, data analysis will occur and any changes to the risk/benefit ratio to study participation will be identified and reported to the IRB. In addition, the PI and co-investigators will meet on an annual basis and reports of the meeting will be submitted to the IRB.

   If an adverse event occurs, it will be reported immediately to the MetroHealth Institutional Review Board (IRB). If an unexpected adverse event occurs, the investigators will assess the risk/benefit ratio of the study and submit any modifications deemed necessary to the IRB for approval. At the time of the IRB renewal, the PI will

submit information about the frequency of the monitoring, the dates that the monthly meeting took place, a summary of the cumulative adverse events, external factors or relevant information that might have an impact on the safety or the ethics of the study, and final conclusions regarding changes to the anticipated risk/benefit ratio to study participation and final recommendation related to the continuation, changing, or termination of the study.

10. Study Assessments

    1. Assessment of presence of neuropathic pain (DN4) at time of admission and discharge
    2. Neuropathic pain levels (Neuropathic Pain Scale, NPS) at time of admission and discharge
    3. Pain scores (NPRS)
    4. Change in pain scores
    5. Opiate use (MME)
    6. Change in opiate use
    7. Average daily change in FIM (calculated [discharge FIM – admission FIM]/LOS)
    8. Change in TMS on the ASIA impairment scale during entire rehabilitation course
    9. Adverse events

        Adverse events will be noted including documented reports of side effects and whether or not drug was stopped due to adverse effects.

11. Amendments
    - If a protocol revision is necessary which affects the rights, safety or welfare of the subjects or scientific integrity of the data, an amendment is required.
    - Appropriate approvals (IRB) of the revised protocol must be obtained prior to implementation.

12. Deviations

    - No changes or deviations from this protocol, except to protect the life and physical well-being of a subject in an emergency will be made.
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13. Potential risk and benefits

    - All the risks are related to the completion of questionnaires and storage of PHI (see Procedure Consent Form).
    - The benefits are all related to the future implications of the study on clinical practice and participation will not impact the subjects directly.

14. Informed consent

- Subject participation in this study is voluntary. Informed consent is required from all subjects\.
- The process of obtaining Informed Consent will follow MetroHealth/IRB process
- Refer to Consent Form

15. Bibliography

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METROHEALTH MEDICAL CENTER
HUMAN INVESTIGATION CONSENT FORM

TITLE:

Comparison of Timing of Initiation on the Efficacy of Gabapentin in Treating Neuropathic Pain in SCI

Introduction

You are being asked to participate in this research study of gabapentin in acute spinal cord injury. Before you can decide whether or not to volunteer for this study, you must be informed of the purpose of the research study, how this study may help you, any risks to you, and what is expected of you. This process is called informed consent.

You do not have to participate in this study. You may stop your participation in this study at any time without changing your current or future relations with MetroHealth Medical Center or its doctors.

If you decide to participate in this study you will be told about any new information learned during the course of the study that might cause you to change your mind about staying in the study. If you withdraw we will still provide you with information regarding possible impacts to your health status or future health care decisions.

Individuals with spinal cord injuries are being asked to be involved in research about a commonly used drug, gabapentin, in effectively treating neuropathic pain.

Why is this study being done?

The purpose of this study is to determine whether or not the timing of the initiation of gabapentin after acute spinal cord injury changes the efficacy of the treatment.

Patients admitted to MetroHealth Rehabilitation Institute with acute spinal cord injury will be asked to participate in this study.

What is involved in the study?

Frequency of Visits –

In this study, you will be asked to participate in two visits, this visit and an additional visit within a couple days of your date of discharge from inpatient rehabilitation. In between, you will be asked to complete a pain diary. Each visit will approximately 20 minutes. The pain diary should take under 1 minute to complete daily. The study visits include:

Screening – Answering questions about yourself and your injury to determine if you are a candidate for the study.

Questionnaires – Answering questions and undergoing one limited physical examination at each of the two visits.

Randomization/study intervention

Treatment with gabapentin for neuropathic pain in spinal cord injury is considered the standard of care. It is not clear at the present time whether early or later treatment with gabapentin is better. For this reason, the timing that the gabapentin will offered to you will be based on chance, the time that you first are treated by a spinal cord injury specialist who starts the medication.

Duration –

This study, will last until you are discharged from inpatient rehabilitation.

What happens if I discontinue or withdraw from the study?

If you withdraw from the study before its completion, you will be asked to specify for what reason so that adverse events may be monitored and reported for patient safety.

Investigator-Initiated Termination of Participation: There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject non-compliance with research, subject not benefiting from research). Your participation might be terminated if you are unwilling or unable to participate in the brief physical examination or answer the questionnaires or report your pain.

What are the risks of this study?

Your participation in this study may involve the following risks:

Emotional and Psychological Risks –

Some of the questions we ask may be upsetting, or you may feel uncomfortable answering them. If you do not wish to answer a question, you may skip it and go to the next question.

Medication –

Although this medication is considered standard of care for neuropathic pain in spinal cord injury, your condition may not improve or may worsen while you are taking part in this study. We cannot predict who may experience potential side effects. You may stop the medication at anytime.

Are there benefits to taking part in the study?

Participation in this research study might be a direct benefit to you. No guarantee of benefit or any other result can be made.

The potential benefits to you from participating in this study may include improved pain control.

Your participation in this study may aid in our understanding of management of acute spinal cord injury and related pain.

What other options are there?

This is a research study. You may decide not to participate.

What are the costs?

There is no additional cost to you or your insurance company for participation in this study.

What happens if I am injured while participating in this study?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur during the course of the study, you must contact your study doctor, Dr. XXXX XXXX at the (216) 778-XXXX . Necessary medical care will be provided to you by The MetroHealth System. The MetroHealth System has not set aside funds to pay you for any such reactions or injuries or for the related medical care. This medical care is not free. You and/or your insurance company will be responsible for the costs. However, you can still try to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the hospital.

Will I be paid for participating in this study?

You will not be paid or compensated for your participation in this study.

What about Confidentiality?

We will make every effort to keep your research records private, but confidentiality cannot be assured. The MetroHealth System has no control over the use of this information once it is released. The information about you that is collected in this study will be shared with the study sponsor and may be combined with information gathered from public sources or other research studies. This information may be used for purposes unrelated to this research and could potentially be used to identify you.

Records that identify you and this consent form may be looked at by a regulatory agency such as:

The Food and Drug Administration (FDA)

Department of Health and Human Services agencies
MetroHealth Institutional Review Board
National Committee for Quality Assurance

If the results of the study are published or presented in public, your name will not be used.

Centralized Data Collection or Registries

The results of your tests will be stored in a centralized computer or data registry at the (name the facility and give the location – the city and state) for [indicate time period].

Storage of tissues and/or blood for the purpose of this study

After tissues and/or blood are collected for this study they will be identified by [indicate how they will be identified].

Storage of tissues and/or blood will be used for future studies not directly related to this study, and may be used to study another condition/disease. [Indicate where the tissues and/or blood will be stored and for how long.]

When Certificate of Confidentiality has been obtained

In this study, you may be asked about illegal activities or highly personal behavior. A Certificate of Confidentiality has been obtained from the federal government. Your study records cannot be subpoenaed [released to courts at their request], and we will only release your study records if you ask us in writing to do so.

What are my rights as a study participant?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you do not take part in the study, your doctor will still take care of you. You will not lose any benefits or medical care to which you are entitled. If you withdraw from the study, with your written permission, clinical data will continue to be collected from your medical records.

If there is DSMB or DMC please add the following language: A Data Safety and Monitoring Board (an independent group of experts) will be reviewing the data from this research throughout the study.

If you chose to take part, you have the right to stop at any time. You will be told of any new findings from this or other studies that may affect your health, welfare, or willingness to stay in this study.

If you are an employee or student, whether or not you take part in this study will not affect your job, current or future medical care, or studies.

[If your study is required to register at ClinicalTrials.gov] A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at any time.

[No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence. There should be a statement that by signing the consent form they are not waiving any of their legal rights.]

Does MetroHealth or any member of the research team have a financial conflict of interest in this study?

The MetroHealth System is NOT being paid to conduct the study.

Whom do I call if I have questions or problems?

If you have questions about any part of the study now or in the future, or if you wish to communicate concerns or a complaint you should contact C. Kim who may be reached at (216) 778-XXXX. If you experience any side effects or injuries while participating in this study, please contact C. Kim, who may be reached at (216) 778-XXXX. For after hours, weekends and/or holidays, call C. Kim, at (216)778-XXXX. If you have any questions about your rights as a research participant, or if you wish to express any concerns or complaints please contact the MetroHealth Medical Center's Institutional Review Board (which is a group of people who review the research to protect your rights) at (216) 778-2021.

Patient/Subject Acknowledgement:

The procedures, purposes, known discomforts and risks, possible benefits to me and to others, and the availability of alternative procedures regarding this research study have been explained to me. I have read this consent form or it has been read to me, and I have been given the opportunity to ask questions or request clarifications for anything I do not understand. I voluntarily agree to participate in this study. I have been given a copy of this consent form.

_____ _____ _____
Patient/Subject Signature Date Time

_____ _____ _____
Signature of Person Obtaining Informed Consent Date Time
(This must be an individual named in the protocol)

_____ _____ _____

Signature of principal investigator or his/her authorized agent Date Time