Ropinirole for the treatment of muscle cramps in patients with cirrhosis

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Principal Investigator: Michael Porayko, MD
Study Title: Ropinirole for the treatment of muscle cramps in patients with cirrhosis
Institution/Hospital: Vanderbilt University Medical Center

Research Protocol

I. Aims

The purpose of the study is to evaluate the efficacy of Ropinirole in treatment of muscle cramps in patients with cirrhosis.

II. Background and Rationale

Muscle cramps are common in liver disease, especially in patients with cirrhosis. The prevalence of muscle cramps among patients with chronic liver disease is estimated to be 22-88%. Patients with cirrhosis who experience muscle cramps report that they are extremely painful and they often occur at rest and frequently during sleep. The severity of muscle cramps in some patients has resulted in presentation to an acute care facility for pain relief with short acting opioids. Muscle cramps impact many areas of life including sleep, physical functioning and mobility, general health, mental health, energy levels and social isolation. Despite the association of muscle cramps with liver disease, there is a paucity of information regarding treatment in these patients. Many treatment options have been reported in the literature but no standard of treatment has been established. Different options include Zinc, 1-alpha-hydroxy Vitamin D, Vitamin E, branched chain amino acids, taurine, L-carnitine, eperisone hydrochloride, intravenous albumin and quinidine. Oral vitamin E replacement has been used successfully in the management of nocturnal muscle cramps in cirrhotic patients. In a group of 23 cirrhotic patients (16 and 7 Child's-Pugh category A and B respectively), oral vitamin E (tocopherol acetate) 200 mg t.i.d. significantly improved the frequency, duration and pain associated with nocturnal cramping without untoward effects. Quinine and quinidine have also been used with success in the treatment of cirrhosis-associated muscle cramps, but their potential for cardiac and gastrointestinal toxicity make them less desirable therapeutic choices. Similarly, another study comparing the effect of 325 mg of quinine versus vitamin E 400 IU at bedtime found reduction in frequency of leg cramps to 3.6 and 3.3% respectively (95% confidence interval, -3.8, +3.2), suggesting similar efficacy. Considering the potential toxicity of quinine, vitamin E is recommended as the initial treatment of choice for patients on dialysis with leg cramps. Our aim is to compare the efficacy of Ropinirole, to Vitamine E in the treatment of these cramps in cirrhotic patients. Ropinirole is primarily used for treatment of restless leg syndrome. However, off label trial of low-dose Ropinirole in clinical practice has shown some success in providing relief of muscle cramps in patients with cirrhosis.

. Procedures

A. **Research Design**: Prospective Randomized cross-over design

B. **Sample**

a. Number of subjects: 60; 30 in Group A; 30 in Group B

b. Inclusion criteria: Patients age >/= 18 years of age with diagnosis of cirrhosis who self-report regular muscle cramping.

c. Exclusion criteria: patients without cirrhosis, patients under age 18, pregnant women

C. **Study procedures**

a. Patients will be recruited from a panel of patients at Vanderbilt University Medical Center Hepatology clinics. Patients meeting inclusion criteria will be randomized to two groups; group A (Vitamin E 400 I.U) or group B (Ropinirole). Patients will remain in their prospective groups until 3 months at which time they will be switched to the other group. Total study duration will be six months. Patient demographics to be collected include patient age, gender, height, weight, BMI, race/ethnicity, etiology of cirrhosis. Baseline lab data to be collected include Magnesium, Potassium, Albumin, and total bilirubin. Child-Turcotte-Pugh class will be calculated using the five measures of severity of chronic liver disease (Total bilirubin, INR, albumin, presence of ascites or hepatic encephalopathy). Baseline data regarding diuretic usage including Furosemide, Spironolactone, Bumex, Metolazone, Inspra will be obtained. A survey (attached) will be given to each group of patients in the beginning of the study period and 3 and 6 months after study initiation.

b. Participants will be given a prescription for Ropinirole. Vitamin E will be provided by the GI clinical research office at no cost to the patients.

c. Adverse event reporting: Serious adverse events will be reported to the VU IRB per VU IRB policy. All adverse events will be captured and reported to the VU IRB at the time of continuing renewal or upon study closure, whichever occurs first.

d. Withdrawal procedures: If a patient suffers an adverse event, which in the judgment of the investigator is an unacceptable consequence or risk to the patient, the patient can be withdrawn from the study. Patients may withdraw from the study at any time for any reason, and without prejudice to further treatment. A patient can withdraw their consent to participate in the study at their own request or be withdrawn from participation in the study at the request of their legally authorized representative at any time for any reason.

e. Privacy and confidentiality issues: Consent will be obtained by the study personnel in a private location within the TVC. No PHI will be collected prior to obtaining informed

consent. The PI and his research staff will have access to this information. Consent forms will be maintained in a locked cabinet in the GI clinical research office. PHI will be collected during the course of this research study from the medical records of consented individuals. Initially, an inclusion log will be created and maintained by the study staff. This log will contain subject initials, medical record numbers, assigned study number and date of inclusion. The only person who will have access to this inclusion log is the PI and study coordinator. The data collected will be entered into a REDCap database (attached) and will not include any information that could link the data to a specific individual. This database will be maintained by the research staff and raw data as well as results will be held by the GI Clinical Research Office indefinitely. The PI, other key study staff and statistician will have access to the REDCap database.

f. Follow up: patients will have follow up at 3 and 6 months after initiation of the study followed by their regularly scheduled appointments after completion of the study.

D. Data Analysis: paired t-test will be used for data analysis**.** Preparation of data listings, tables, and overall statistical support for generation of the data will be managed independently by a statistician who will remain isolated from the clinical personnel involved in the study operations.

IV. Bibliography

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