Diabetic Complications Consortium

Application Title: Thoracic Splanchnic Magnetic Neuromodulation Therapy (ThorS-MagNT) for Grade 3 Diabetic Gastroparesis: Pilot Study

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1. Project Accomplishments:

The goal of this study is to examine a non-invasive peripheral nerve treatment using repetitive magnetic stimulation, Thoracic Splanchnic Magnetic Neuromodulation Therapy (ThorS-MagNT), in a proof-of-concept study in patients with Grade 3 diabetic gastroparesis (DG). The aims are to evaluate the safety, effectiveness, and feasibility of ThorS-MagNT in patients with Grade 3 DG and to evaluate predictive factors of treatment. Our central hypothesis is that ThorS-MagNT will improve sympathetic hypofunction, gastric hypomotility/atony, and spino-gut interactions and thereby improve symptoms of DG.
This single center clinical research study was established with a project period of 11/01/20 – 10/31/21 and a budget period of 11/01/20 – 06/30/21. In the first year we have accomplished the following tasks: 1) Designing/refining ICD, CRFs, and PRO forms; 2) Securing regulatory approvals, from Augusta University; 3) Training research staff, Post-docs and others on study activities; 4) Recruitment, enrollment, and performance of 7 ThorS-MagNT study in patients with diabetes gastroparesis; 5) Weekly 2 hour lab meetings and monthly meetings with study consultant (Dr. Satish Rao) and oversight; 6) Submitting abstracts for national level meetings. These are accomplishments are described in more detail below.

1. Designing/Refining ICD, CRFs, and PRO forms: In consultation with biostatistician (Dr. Deepak Ayyala), and IRB experts, starting in June 2020, and before grant funding we revised all CRFs and PRO forms. For this study we created a 14-page detailed ICD and 12 CRF / PRO forms. We also to create a Manual of Procedure (MOP) for this study to be used as the referral source by all study staff. AU study team spent 2 months to create and fine tune the treatment procedure carefully detailing all aspects of the protocol and procedures following NIH guidelines.

2. Securing regulatory approvals, from Augusta University: we submitted our study to AU IRB on 23rd June 2020 to head start the regulatory approval process, before grant was funded. Because this is a novel pilot there were many amendments and modifications to be made and after much deliberation, AU IRB approved study on 23rd October 2020. Subsequently, OnCore opened the study, study was registered in clinicaltrials.gov, and first patient was enrolled on 7th December 2020.

3. Training research staff, post-docs, and others on study activities: Dr. Sharma conducted teaching and training of all study staff, Post doc, research coordinators and research technician on all study-related procedures and CRFs in November 2020 after AU IRB approval. These training sessions were designed to cover all aspects of the protocol, all the procedures and regulatory compliance required by the AU IRB. Dr. Sharma personally supervised conduct of all procedures and implemented quality assurance.

4. Recruitment, enrollment, and performance of ThorS-MagNT study: The ongoing COVID pandemic has significantly affected recruitment particularly early in 2021 as AU site closed

clinics in January and February 2021. Hospital was full of COVID patients and research team felt it was advisable not to admit patients for research only. Further the COVID related restrictions also affected patient's ability to participate and travel to hospitals for fear of catching illness. In the first year we have enrolled and treated 7 patients.

5. Weekly 2-hour lab meetings monthly meetings with study consultant (Dr. Satish Rao) and oversight: We have conducted 30 weekly lab meetings at AU and reviewed recruitment, protocol issues, regulatory concerns safety, budget and adverse events. Dr. Satish Rao, consultant for the study, met with the team to discuss study protocol, regulatory and data acquisition and quality, and he participated in the weekly meetings as well.

6. Submitting abstracts for national level meetings: We submitted abstracts of the preliminary results of the study for 3 national level meetings namely, 2021 American College of Gastroenterology (ACG) Annual Scientific Meeting held in Las Vegas, North American Neuromodulation Society (NANS) 25th annual meeting in Orlando, and Digestive Disease Week 2022 in San Diego. The abstract from the ACG Annual Meeting has been published (citation below).

2. Specific Aims:

Specific Aim #1 – Evaluation of the Safety and Effectiveness of Thoracic Splanchnic Magnetic Neuromodulation Therapy (ThorS-MagNT) in patients with Grade 3 Diabetic Gastroparesis. To test the hypothesis that ThorS-MagNT will reduce symptoms of gastroparesis, improve gastric emptying, and is well-tolerated. ThorS-MagNT is performed by low-frequency, low-intensity repetitive magnetic stimulation bilaterally around T7-8 intravertebral space twice a day for 5 days with a total 1200 magnetic stimulations per treatment session at 1 Hz. The primary outcome is responder rate, defined as ≥20% reduction in the Gastroparesis Cardinal Symptom Index-daily diary (ANMS GCSI-DD) score. Secondary outcomes include subscores of the ANMS GSCI-DD, effects on gastric emptying time, Patient Global Impression of Improvement (PGI-I), safety, and tolerability.

Results: Seven DGE patients (6F; 1M) were enrolled, tolerated treatments, and completed the study. Subjects (n=4) treated at optimal intensities of 150% motor threshold had an average of 74.9% reduction in total ANMS GCSI-DD score from baseline versus 10.1% reduction in subjects treated with lower intensities. Symptom improvement persisted 2 weeks post-treatment with an average of 97.9% reduction in total ANMS GCSI-DD score from baseline versus 0.3% reduction in subjects treated with lower intensities. One subject with known hypertension experienced medication-related hypotension unrelated to study treatment. After resuscitation, this subject completed 4 remaining treatments. Another subject reported self-limited tingling and numbness, which resolved after treatment. No other adverse events occurred.
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Specific Aim #2 – Determination of predictive factors for response to ThorS-MagNT for Diabetic Gastroparesis. To test the hypothesis that subjects with more severe disease as assessed by the Patient Global Impression of Severity (PGI-S), poorly controlled diabetes, increased BDNF, and significant neuroinflammation will predict better response to ThorS-MagNT.

Results: We have collected and stored pre- and post- treatment serum samples from all the subjects. We will run the samples once we have collected all the samples. Also, we will run a correlation analysis once we have increased our sample size.

3. Publications:

1. Sharma A, Karunaratne TB, Yan Y, Eubanks A, Inman B, Rao S. S1440 Novel Neuromodulation Treatment Using Repetitive Magnetic Stimulation for Diabetic Gastroparesis: Preliminary Results From a Proof-of-Concept Study. Official journal of the American College of Gastroenterology| ACG. 2021 Oct 1;116:S661.