Title	A Randomized Controlled Trial for Transcutaneous Magnetic Stimulation of the Stellate Ganglion to Treat Ventricular Tachycardia Storm
Date	06/04/2022
NCT Number	04043312
Short Title	Magnetic Stimulation for Electrical Storm
Phase	Randomized Controlled Trial
Methodology	Two arm, randomized sham controlled trial to assess the efficacy of transcutaneous magnetic stimulation of the left stellate ganglion to treat patients with ES.
Study Center(s)	Single-center
Number of Subjects	Twenty-six (26) subjects are expected to be enrolled
Inclusion and Exclusion Criteria	Inclusion Criteria: Age >18 years, ≥ 3 episodes of VT in 24 hours Exclusion Criteria: Pregnancy, planned ablation with in 24 hours, implanted ventricular assist device, metal implanted in head or neck (except the mouth), implanted medication pumps, cochlear implant, implanted brain stimulator, ocular implant, history of malignancy in neck (region of stimulation)

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including the following regulations as they apply 45 CFR 46, 21 CFR Parts 50, 54, 56,and 812. All episodes of noncompliance will be documented.

Introduction

1.1 Background and Relevant Literature

Cardiac electrical storm (ES) is a medical emergency characterized by three or more episodes of ventricular arrhythmia within 24 hours and associated with a significantly increased mortality and massive health resource utilization. While the mechanism of ES is variable, it is likely induced by a complex interplay of triggers (e.g. electrolyte abnormalities), autonomic dysfunction, and an abnormal electrophysiological substrate. Several therapies are utilized including sympathetic blockade (through deep sedation and beta blockers), antiarrhythmic drugs, implantable cardioverter defibrillator (ICD) reprograming where applicable, and catheter ablation. Despite standard intervention, mortality rates remain high and additional therapeutic options are actively being investigated.

Numerous lines of evidence have suggested the therapeutic benefit of autonomic modulation for the treatment of ventricular arrhythmias. In 1916, Thomas Jonnesco first performed a left sympathetic denervation for incapacity angina and life-threatening cardiac arrhythmias (1). Since that time, cardiac sympathetic denervation (CSD) has been used to successful treat patients at high risk for sudden death due to congenital long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, or post-myocardial infarction (2, 3). Given the dominance of left sided sympathetic nerves innervating the ventricle, left CSD has been utilized more commonly, although bilateral CSD is also used (4). The number of indications with evidence of benefit continues to grow and includes hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and ES (5-7).

More recently, the surgical technique for CSD has improved with a minimally invasive thorascopic approach and non-surgical strategies for sympathetic denervation have also been employed (8-10). Although large prospective trials have not yet been conducted, there is growing evidence that stellate ganglion blockade (SGB) is an effective therapy for ES. This procedure is performed by injecting local anesthetic agents percutaneously into the stellate ganglion generally via anatomic, ultrasound, or fluoroscopic guidance. The goal, similar to CSD is to reduce cardiac sympathetic tone to improve short-term control of ventricular arrhythmias and the need for defibrillation. While the anesthetic agents would be expected to have a short duration of effect based on their half-life, patients seem to experience an extended duration free of arrhythmia, possibly secondary to favorable remodeling of the highly plastic nature of the autonomic nervous system (10-12). A non-invasive approach to block the autonomic input from the stellate ganglion could, therefore, be a valuable option to treat ES.

1.2 Name and Description of the Investigational Product

The investigational device used will be transcutaneous magnetic stimulator produced by Magstim Company Limited (Magstim SuperRapid). The device utilizes current to produce an electromagnetic pulse that is delivered at low frequency to the stellate ganglion as described below. This system is FDA 510(k) approved for the stimulation of peripheral nerves. rTMS systems are considered by the FDA to be Class II medical devices. Given the clinical data described below, low frequency cervical magnetic stimulation does not pose significant health risks.

1.2.1 Nonclinical Data

There is relevant animal model data on the impact of sympathetic magnetic stimulation on atrial fibrillation and ventricular arrhythmias. In 2004, Scherlag et al. applied high frequency (2kHz) magnetic stimulation to canine vagosympathetic trunks, demonstrating the ability to induce atrial fibrillation (AF). They additionally applied low frequency (0.04 Hz) magnetic stimulation across canine chest, inducing 2:1 AV block and making AF non-inducible for several hours (13). This result was re-demonstrated recently, with low frequency (0.952 Hz) and extremely low intensity ($3.4x10^{-12}$ Tesla) magnetic stimulation to canine cervical vagal trunks and across chest walls inhibiting AF inducibility for hours (14). These animal studies fit with a growing body of evidence that autonomic modulation can be used to treat AF. This includes ganglion plexus ablation or botulinum toxin injection, spinal cord stimulation, and renal artery denervation (15-18). Low-level electrical vagal nerve stimulation has proven especially promising in animal studies, reducing inducibility of AF, preventing AF development in obstructive sleep apnea rabbit models, and even reversing atrial remodeling (19, 20). A canine study of low-frequency (1 Hz) magnetic stimulation applied over the left stellate ganglion at 90% of the local motor threshold recently showed the ability to prevent ventricular arrhythmias in the setting of acute myocardial infarction (21). These results suggest that the beneficial effects of sympathetic modulation via CSD or SGB may be reproducible with non-invasive and painless magnetic stimulation.

1.2.2 Clinical Data to Date

To date, there is no clinical data on magnetic stimulation for the treatment of arrhythmias, including ventricular tachycardia or ES. There is, however, extensive clinical data on the safety and efficacy of TMS for neurological and psychiatric disease as well as percutanesous cervical magnetic stimulation for phrenic nerve stimulation and promotion of bone growth following spine surgery.

The majority of safety data comes from the TMS literature, which has been referenced in the use of peripheral stimulation as well given the similar physical properties. The primary concern of TMS systems has been heating, which is an unavoidable consequence of the generation of current. Air or oil coiling systems can be put in place were necessary to avoid excessive heating of the coil and commercially available coils have heat sensors and automatic shut-off systems in place (22). Excessive heating is of less of a concern with the use of exclusively low-frequency stimulation. Attractive force and heating of ferromagnetic objects is also a theoretical concern. This includes aneurysm clips in the brain, which do not appear to be significantly affected by TMS, as well as cochlear implants and deep brain stimulations, which are considered contraindications to TMS (22).

For magnetic therapy of cardiac arrhythmias, implanted cardiac devices pose a potential concern. TMS is considered safe in the presence of implanted cardiac devices, along with vagal nerve stimulators and spinal cord stimulators as long as the TMS is not activated over the components in the chest. There is literature on the safe use of TMS in patients with implanted cardiac devices - no effect on device function has been noted (23, 24). Furthermore, according to the recent safety consensus statement, TMS is considered safe in individuals with cardiac pacemakers (22). Peripheral magnetic stimulation generally produces the same approximate magnetic intensity of a 1.5-Tesla MRI scanner and often substantially less (13, 22). Notably, in our feasibility study discussed below, no subject received more than 35% of the maximal device capacity (1.2 T) during the stimulation protocol. Patients with implanted cardiac devices are able to safely have 1.5 Tesla MRIs performed when the magnetic stimulation is directed directly over the device in the case of chest MRI (25). As we will not be stimulating over any device components (which are located in the chest, not the neck) we feel that our protocol can also be safely performed in this patient population just as it is for TMS.

Nevertheless, additional precautions will be taken as described in our protocol. For enhanced safety, patients with implanted cardiac devices in our study will undergo reprogramming and monitoring of the ICD as previously validated for magnetic resonance imaging studies where the device is exposed to magnetic fields. Prior to stimulation, the device will be interrogated to determine normal function and parameters as well as underlying heart rhythm and possible dependence on pacemaker function. Any patients with abnormally functioning devices at baseline will be excluded. All tachycardia therapies will be turned off during the protocol to prevent inappropriate delivery of therapy. In the event of pacemaker dependence, the device will be set to an asynchronous pacing mode to prevent the magnetic stimulation from inappropriate inhibiting necessary pacing. Following the procedure, during which an Advanced Cardiac Life Support (ACLS) trained provider will monitor the patient closely as per our initial protocol design, the device will be re-interrogated to determine any change in function or parameters. Tachycardia therapies will be turned back on as appropriate after completion of the protocol (25, 26).

It is also important to note that TMS has not been studied in pregnant patients.

Relevant safety data from peripheral magnetic stimulation comes largely from phrenic nerve stimulation, which it is used for respiratory muscle weakness. Cervical magnetic stimulation has been performed to stimulation the phrenic nerve for decades using 1.5 T magnets without significant adverse effects and is reportedly painless (27-29). It has also been used in intubated patients (30). Phrenic nerve magnetic stimulation has also been safely performed with application directly over the upper sternum (30). Interesting, a CervicalStim device is a commercially available device used to aid in bone healing after cervical-spine fusion. This device has been shown to safely deliver high frequency (3.85 kHz), low intensity (1.19×10^{-6} Telsa) to the posterior cervical spine (31, 32). The presence of implanted cardiac devices is considered a warning but not a contraindication to its use.

2 Study Administration, Data Handling and Record Keeping

2.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

2.2 Data Collection and Management

Study data will be imported in to MS Excel following each enrollment. The PI and co-investigator will have access to this data. To retain confidentiality, the data will be stored on an encrypted flash-drive. Within 6-months of study completion, the data will de-identified to retain confidentiality going forward. The data will be stored, de-identified, for up to 5 years.
Signed consent forms will be retained in a locked file cabinet.

2.3 Records Retention

Records, including signed consent forms will be retained for at least 3 years following the completion of the study. After three years, the signed consent forms will be effectively destroyed.

3 Study Monitoring, Auditing, and Inspecting

3.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan described above. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

3.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities.

4 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

4.1 Risks

The risks of the magnetic stimulation protocol include change in blood pressure or heart rate, induced arrhythmias, and patient discomfort. None of these changes were apparent in the 5 patients enrolled in the feasibility study. Subjects will be monitored for each of these during the protocol and it will be terminated as described above. As cervical magnetic stimulation has been performed in other patient populations without the aforementioned adverse effects, we believe the risks posed will be minimal.

Additionally, for subjects with implanted cardiac devices, the risks include device malfunction. Devices will be interrogated before and after the protocol to ensure normal functioning. Notably, the stimulation will not be directed at the devices, consistent with consensus statement guidelines for TMS. Using the same protocol for interrogation and reprograming, magnetic resonance imaging can be safely performed and we believe the proposed magnetic stimulation protocol poses minimal risk in these subjects.

4.2 Benefits

Direct Benefits:

- Decreased burden of arrhythmias.

Indirect Benefits:

- Development of a novel treatment for cardiac arrhythmias, benefiting society as a whole.

4.3 Risk Benefit Assessment

The risks of participating in the study are outweighed by the potential benefits of participating in the study.

4.4 Informed Consent Process / HIPAA Authorization

- Primary or co-investigator will obtain informed consent with signature of the consent form.
- The consent process will take place in the hospital or over the phone if patient is unable to consent and health care decision maker is not in the hospital. If the subject is able to provide verbal consent but unable to sign the consent form, a witness to verbal consent will sign the form.

- During the consent process, subjects or health care decision maker will read-back all risks to ensure comprehension of the study. Where applicable, the legally authorized representative will be provided with the informed consent form to read and sign.
- Prior to consent, subjects will be assured that there will be no change in the clinical care received if they decline to participate.
- Subject's privacy will be assured with all consent forms and clinical information securely maintained.
- Consent will take place at the time of initial discussion regarding enrollment.

5 Safety and Adverse Events

5.1 Definitions

5.1.1 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

5.1.2 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

5.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module

of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

5.3 Relationship of AE to Study

The primary investigator will determine the relationship of each adverse event to the study procedure. The relationship will be classified (definitely related, probably related, possibly related, unlikely, or unrelated).

5.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

All reportable adverse events will be reported per the Penn IRB guidelines. All reports will include the following information:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below.

5.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

5.4.2 Investigator Reporting: Notifying the Penn IRB

Reportable events will include any adverse event or incident that has the potential to be classified by the IRB as an unanticipated problem posing risks to participants or others. This includes incidents events that are both unexpected in nature or severity and probably or definitively related to participation in the research study, which will be determined by the primary investigator. All such events will be reported to the IRB within 10 business days of discovery. If the event involved a death and indicates that others are at increased risk of harm, the report will be filled within 3 days. Notification will occur using a Reportable Event Form.

5.5 Stopping Rules

If sustained ventricular arrhythmia or hemodynamic compromise (defined as a drop in systolic blood pressure >20 mmHg or need for additional inotropic support) occurs during the protocol, it will be terminated. Additionally, if the subject requests the protocol be discontinued for any reason, it will be terminated.

If any protocol is terminated before completion, further enrollment will cease until the primary investigator can evaluate the event in order to determine whether a significant safety risk was posed. If the intervention is felt to be probably or definitively associated with a significant safety risk, the IRB will be contact prior to continuing enrollment.

Investigational Plan

Subjects will be screened using intensive and cardiac care unit census lists in the EMR to identify patients meeting inclusion and exclusion criteria. Potential subjects will be discussed with primary clinical team prior to approaching. If the primary team feels enrollment is appropriate, subjects or their decision maker will be approached for consent. Written (or telephone consent when necessary) will be obtained before beginning the study protocol.

Once screening and consent are complete, the subject will be randomized to the intervention or sham-control arm. Following randomization, intervention phase will begin. A 12-lead ECG will be performed and continuous telemetry monitoring will be activated prior to positioning the rTMS coil at the base of the left neck directed in approximation of the left stellate ganglion.

For subjects randomized to the intervention arm, the rTMS system will then be activated at the maximal device intensity. If local muscle contraction is noted, the intensity will be decreased in 10% increments until contraction is no longer present. Once the motor threshold is determined, the intensity will be set to 80% of this threshold. If local muscle contraction is not noted at the maximal intensity, the setting will be set to 80% of the maximal intensity. Stimulation will then continue at a frequency of 0.9 Hz for 60 minutes. Blood pressure and perfusion index will be assessed every 5 minutes during stimulation. Following stimulation, a repeat 12 lead ECG will be performed. If applicable, patients will be asked whether they experience discomfort during the stimulation.

For subjects randomized to the sham-control arm, the rTMS coil will be positioned with the back of the coil housing in contact with the subject – under this condition there will be an auditory artifact but no stimulation. To mimic the threshold determination, ten (10) individual pulses will be delivered at varying intensities by the machine prior to beginning 60 minutes of pulses at 0.9 Hz delivered at the minimal intensity of the system.

Subjects, their primary clinical team, and the physician assessing arrhythmic outcomes will be blinded to their treatment arm for the duration of the study period.

Telemetry monitoring for arrhythmias will be performed daily for either 72 hours after the intervention phase or until hospital discharge if that occurs earlier.

Primary Study Endpoints

The primary endpoint will be freedom from VT in the 24-hours following randomization.

Secondary Study Endpoints

- Number of episodes of VT or NSVT in the 72-hours following randomization.
- Change in ICD/pacemaker parameters
- Change in blood pressure, heart rate, perfusion index, palm temperature during the stimulation protocol
- Change in PR, QRS, and QTc interval from pre- and post-intervention ECGs
- Presence of local skin irritation at the site of stimulation
- Subjective reported discomfort from stimulation (when applicable – i.e. non-sedated patient) assessed post-intervention with scale 0-10.
- Mortality, duration of ICU hospitalization, antiarrhythmic drugs used, and ablation procedures performed

Safety Evaluations

During the stimulation protocol, heart rate will be monitored by continuous telemetry and blood pressure will be checked every 5 minutes by automatic cuff or arterial line when present. Following completion of the protocol, subject discomfort will be assessed as above when possible. In patients with an implantable cardiac device, interrogation and re-programming will be performed before and after the protocol as above.

If sustained ventricular arrhythmia or hemodynamic compromise (defined as a drop in systolic blood pressure >20 mmHg or need for additional inotropic support) occurs during the protocol, it will be terminated. Additionally, if the subject requests the protocol be discontinued for any reason, it will be terminated.

Duration of administration (if applicable)	Each subject will receive a single 60-minute session of magnetic stimulation or sham magnetic stimulation based on their randomly assigned treatment arm.

Reference therapy	Standard therapy for ES is variable but often includes antiarrhythmic drugs, sedation, and catheter ablation. rTMS will be provided in addition to standard appropriate therapy for patients randomized to the rTMS arm. In patients randomized to the control arm, standard therapy alone will be provided in addition to sham stimulation.
Statistical Methodology	Based on the results of our feasibility study and available literature, we anticipate 80% of patients in the control group and 20% of patients in the TcMS group will have VT in the 24 hour period following randomization. Assuming alpha 0.05, a hazard ratio of 0.40, and a sample size of 26 subjects, we estimate study power to be greater than 80%. Differences in outcomes between arms will be compared using χ^2-tests or fisher's exact test for categorical variables and analysis of variance for continuous variables. Subject characteristics and outcomes will be described using mean and standard deviation. Non-parametric statistical hypothesis tests will be used when the data are not normally distributed. Poisson regression will be used to evaluate the burden of recurrent VT. All statistical tests will be 2-sided, with $p<0.05$ indicating statistical significance.

6 References

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