A controlled prospective observational study of recurrent syncope with the use of an implantable loop recorder in patients who manifest tilt table induced asystole

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A. Study Purpose and Rationale

This investigation is intended to study a population of patients that manifest an abnormal response to a tilt table study. Tilt tables are used in the diagnosis of patients with a history of syncope. Patients who have a positive response on the tilt table are thought to have a specific type of syncope termed "neurocardiogenic" or "vasovagal" syncope. A subset of patients who test positive for neurocardiogenic syncope manifest a period of asystole. Asystole is a period of time when the heart ceases to beat and is defined in this study as a pause of greater than or equal to five seconds. Not surprisingly, physicians become particularly concerned when a patient's heart beat pauses in the setting of a relatively innocuous diagnostic test. This study will observe a population of patients who manifest "tilt-induced" asystole over a period of one year and compare outcomes with a control population consisting of patients who test positive for neurocardiogenic syncope on the tilt table but do not manifest asystole. The primary outcome to be measured is incidence of recurrent syncope defined as one or more syncopal events during the follow up period as reported by the patient. Secondary outcomes include all cause mortality, cardiac specific mortality, and the proportions of three specific arrhythmias that occur at the time of recurrent syncope in cases versus controls. Specific arrhythmias (asystole, bradycardia, and tachycardia) are to be monitored in each patient with the use of an implantable loop recorder (ILR). This device (Reveal Insertable Loop Recorder, Medtronics AVE, Santa Monica, California), already being used in clinical practice, is an electrical monitor that is surgically implanted in the subcutaneous tissue. It monitors a continuous recording of cardiac electrical activity and stores selected periods of activity in a memory bank when prompted by the patient. This stored memory can then be reviewed by a physician at a later date.

The hypothesis of this study is that patients who manifest "tilt-induced" asystole have a poorer prognosis relative to patients with neurocardiogenic syncope who do not manifest "tilt induced" asystole with the outcomes mentioned above. Should this hypothesis prove true, it may lend support to the notion that patients who become asystolic on the tilt table should be treated more aggressively with either pharmacologic agents or permanent pacemakers.

B. Study Design and Statistical Analysis

This is a controlled multicenter prospective observational study. Cases will be defined as patients who manifest tilt induced asystole. Controls will be defined as patients who test positive for neurocardiogenic syncope on the tilt table test but do not manifest asystole. Controls will be matched with cases for the following characteristics: age, gender, and number of previous syncopal episodes (i.e. 1, 2-4, 5 or greater). Cases will be enrolled on a consecutive basis from multiple centers. Controls will be enrolled at a chronological time that coincides as closely as possible with each matched case enrollment. Exclusion criteria for cases and controls include: history of secondary causes of syncope including CAD, LV dysfunction, cardiac valvular disease, and CVD.

There have been only a handful of studies that have addressed this clinical question in the past [1-12]. Most studies involved a small number of cases (10 to 50) and hence did not detect statistically significant differences between cases and controls. The largest study to date was conducted by Baron-Esquivias et al[(11)] who studied 58 patients with tilt induced asystole. The cohort was studied relative to a gender and aged matched control. Over a mean 40.7 months of follow up 20.6% of the cohort

experienced recurrent syncope relative to 28.8% of controls (p = NS); the conclusion being no difference between the two groups. The difficulty with this study was that many of the case patients where treated during the study with either pacemakers or medications making comparison to the control population difficult. Given the lack of data on the true rate of recurrent syncope in the case population, some inferences will be necessary for the purpose of powering this study. Data on the incidence of recurrent syncope in the control population from pooled studies[12] is known to be around 35%. Taking a clinically significant absolute difference between cases and controls to be around 10% (i.e. 45% of tilt-induced asystolic patients will have recurrent syncope), a study powered at 80% with an alpha value of 0.05 will require to following number of cases and controls using the Chi Squared test.

Cases: n = 560
Controls: n = 560

Or, taking two matched control per case, one may reduce the case number to half this value which is fortunate given the relative rare prevalence of tilt positive asystolic patients detected in a tilt table lab.

Cases: n = 280
Controls: n = 560

At the conclusion of the study, data analysis will include comparing proportions of events between the two groups. Statistical significance will be assessed by the Chi Squared test with a p value threshold set at 0.05.

C. Study Procedure

At the time of enrollment, after informed consent is obtained, patients are to undergo a more complete history and physical. Within 24 hours of enrollment they are then to receive an implantable loop recorder. The implantable loop recorder (ILR) is an electrical monitoring device that is approximately the size of a pack of gum. It is implanted by a physician into the subcutaneous tissue under local anesthesia in the upper portion of the chest (two fingerbreadths inferiorly to the left clavicle). This procedure is done on an outpatient basis and usually requires 20 minutes to complete. There is minimal discomfort to the patient during the procedure. It is currently being used in clinical practice to ascertain the etiology of syncope in patients who remain undiagnosed after a conventional work-up though to place an ILR in every patient after a positive tilt test in not standard of care and would be done in this instance for research purposes. Incidence of complications of the implantation (i.e. infection and bleeding) have not been reported.

The device monitors the heart rhythm continuously. After the patient experiences a syncopal event, and regains consciousness, a small magnet the size of a pager that the patient carries on his or her belt is placed on the skin overlying the ILR. This enables the ILR to store the prior seven minutes of heart rhythm into a memory bank. In a timely fashion (after the patient has been properly assessed for the syncopal event), the ILR is interrogated to assess the rhythm that coincided with the event (if any). The ILR may then be removed if an arrhythmogenic etiology is discovered and appropriate treatment is instituted. Of note, the device may be left in for up to one year if no arrhythmia is discovered during the study.

At the inception of the study, follow up will be scheduled at one week (to assess for the absence of infection at the ILR site), then again at four months intervals (to assess tolerance of the device) for a total follow up period of one year. A diary is to be kept of the timing of all syncopal episodes to corroborate with the events logged on the ILR. During the study time period, each patient will be allowed to return to normal follow up with his or her regular physician and no restrictions will be placed on any further diagnostic or treatment modality.

D. Study Drugs

N/A

E. Medical Device

The implantable loop recorder (ILR) is a commercially available, FDA approved device manufactured by Medtronics AVE, Santa Monica, California. It is 61 mm long, 19 mm wide, and 8 mm thick. It weighs 17 grams. After local anesthesia, the device is inserted two fingerbreadths below the left clavicle via a 2 cm incision with blunt finger dissection of the subcutaneous tissue. The device is sutured to the underlying pectoralis muscle and the pocket is closed with fine sutures. This device has existed in clinical use since 2001 and there has yet to be a reported complication. The cost of the device itself is estimated at $2500. The device monitors heart rhythm for up to 14 months and when activated by a magnet placed on the overlying skin by the patient (after a syncopal event has occurred and the patient has regained consciousness), it records the prior seven minutes of cardiac activity into its memory bank. From this point, the device can be interrogated remotely to assess the culprit rhythm. At the end of the study, the device is removed using forceps after another small incision is made into the overlying skin.

F. Study Questionnaires

A standard template diary will be distributed to each subject. The diary will include the patient's unique identification number at the top with space provided to register time of onset, duration, and symptoms of each syncopal episode as well as a space to record presence or absence of ILR activation during the event.

Due to the size of the study, multiple centers will be recruited with a study director designated at each center (typically the center director of the tilt table laboratory). Patient follow up will be conducted by a team formulated by each center's study director. Each team will typically consist of the center director, associated cardiologists with experience in the tilt table laboratory, as well as nurse practitioners, registered nurses, and physician assistants trained in the appropriate data collection to be conducted at each follow up visit. Of note, the first visit (one week after implantation of the ILR) will be conducted by the physician who had performed the procedure to assure patient safety.

G. Study Subjects

Cases will be defined as patients who manifest neurocardiogenic syncope with asystole of greater than 5 seconds on the tilt table. Controls will be defined as patients who manifest neurocardiogenic syncope without asystole on the tilt table. Controls will be matched with cases for age, gender, and number of previous syncopal episodes.

Exclusion criteria will include secondary causes of syncope including known CAD, LV dysfunction, CVD, and cardiac valvular disease. Patients with pacemakers already implanted as well as patients on beta blockers will also be excluded as to control for confounding. Patients less than 18 years of age will not be included in the study (unable to give informed consent due to their minor status). Patients who lack the mental capacity to (1) reliably record in a diary the timing and characteristics of a syncopal event and (2) activate the ILR will be excluded. Due to the as yet unreported but potential complications of the ILR (infection, bleeding) and the use of local anesthetic for its implantation, pregnant women will be excluded from the study and all women enrolled in the study of child bearing age will have a urine pregnancy test prior to enrollment. A woman who should become pregnant during the study will continue to be followed as they will be well out of risk period of complications from the ILR.

Otherwise, cases and matched controls are to be enrolled on a consecutive basis without regard for gender, race, and ethnicity.

H. Recruitment of Subjects

Potential cases will be identified after manifesting tilt-induced asystole. The physician interpreting the tilt table study, after discussing the interpretation and the recommendations for further diagnostic work-up or treatment via standard clinical practice, will then approach the patient concerning enrollment. Permission for enrollment will also be sought from the patient's primary referring physician. Informed consent for the procedure will then be obtained after full disclosure of the study design and purpose. Matched control will be recruited in a similar fashion. Each control will be sought at a chronological time that coincides as closely as possible with case enrollment (i.e. the case and matched control tilt table study will coincide to within two weeks of one another).

I. Confidentiality of Study Data

All study data are to be coded with a unique identifier number. The master list pairing the unique identifier number with the patient's demographic data will be safeguarded by each center's study director and kept is a secure location accessible only to the study investigators.

J. Potential Conflict of Interest

Partial funding for this multicenter study will come from Medtronic, Inc. No study investigator will receive any form of compensation from Medtronic, Inc. for participation in the study. All potential center study directors will perform full disclosure of any conflict of interests including holding stock in the Medtronic corporation or any current or past monies received by the Medtronic corporation for duties rendered.

K. Location of the Study

Recruitment, placement of the ILR, and follow up are all to be conducted at each center's tilt table laboratory equipped with a standard tilt table, ancillary monitoring equipment, appropriate pharmacologic and resuscitative devices, as well as private clinical rooms for ILR placement and follow up. Each IRB at its respective institution will be presented with a protocol for approval. No enrollment will be initiated at any center without approval by the respective IRB.

L. Potential Risks

There is a potential for infection and bleeding when a device is implanted in human tissue though this complication has yet to be reported. In addition, there is a small risk of allergic reaction to local anesthesia. An allergy history will be obtained from each patient and all study subjects will have close follow up with study investigators to assess tolerance of the device.

M. Potential Benefits

A benefit of ascertaining a likely etiology of recurrent syncope in both cases and controls via use of an ILR is present. In many instances, the etiology of syncope is never fully elucidated in patients who manifest recurrent symptoms. The use of an ILR is gaining much popularity in routine clinical usage to delineate cause of syncope in patients who either have negative conventional diagnostic work-ups and in those who test positive for neurocardiogenic syncope on the tilt table but fail to respond to therapy with medications or pacemakers. Concerning subjects enrolled in this study, it is likely that an arrhythmogenic cause of recurrent syncope will be elucidated in a significant proportion of cases and controls thereby leading to a more rational mode of treatment. This data will be collected at no cost to the patient.

N. Alternative Therapies

N/A

O. Compensation to Subjects

Given the proposed benefit of the data from the ILR on both cases and controls that will be provided at no cost to the patient, no additional compensation other than travel costs (i.e. parking validation or reasonable mass transit commuter fares) will be provided. Travel costs for each follow up visit will be provided at the end of each follow up encounter. In addition, should any complication arise from the ILR, full assessment and treatment of the complication will be assumed by the study budget.

P. Cost to Subjects

Parking validation or reasonable mass transit commuter fares will be provided to each subject, otherwise further travel costs will have to be assumed by the individual patient for follow up visits.

Q. Minor as Research Subjects

N/A

R. Radiation or Radioactive Substances

N/A

S. References

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