Assessing the Efficacy of Midodrine in Improving Orthostatic Tolerance Using Lower Body Negative Pressure plus Tilt-Table Testing

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A. Aim

To assess the effect of midodrine, an FDA approved drug for orthostatic hypotension, on vasovagal syncope using lower body negative pressure plus tilt-table testing.

B. Background and Significance

Syncope ("fainting") is defined as a transient loss of consciousness due to reduced cerebral blood flow (1) It is a major clinical problem in the U.S. population. It is estimated that approximately 3% of emergency department visits and 2-6% of hospital admissions are for syncope (1), with more than 500,000 new patients experiencing syncope per year (2) and costing the health care system over $2 billion annually (3).

Although the causes of syncope are numerous, and include disorders of vascular tone or blood volume, cardiovascular disorders, and cerebrovascular disorders, the type of syncope to which this study pertains is orthostatic intolerance, or syncope resulting from the stress of standing erect (e.g. orthostatic stress) due to excess blood "pooling" in the veins of the lower extremities, thus reducing systemic and cerebral blood flow and inducing syncope. When a healthy person stands erect, this venous pooling is compensated by three physiologic mechanisms, largely regulated by the autonomic nervous system: constriction of arterioles and venules, increased heart rate, and contraction of the leg muscles, which serve as a pump to increase venous return. However, patients with orthostatic tolerance are deficient in one of these mechanisms, and thus can not compensate effectively when standing and are prone to syncope.

Orthostatic intolerance can further be grouped into three categories. The first is acute orthostatic hypotension, during which the patient experiences an acute drop in blood pressure when standing that can eventually lead to syncope. The second category is dysautonomic syncope, where the patient experiences a slower, progressive drop in blood pressure that eventually leads to a syncopal event. The final category is vasovagal syncope, which occurs when a patient initially experiences appropriate responses to a decreased systemic blood volume, such as the normal compensatory mechanisms outlined above, but eventually very low ventricular volumes lead to mechanoreceptor activation and an increased parasympathetic stimulus called the Bezold-Jarisch reflex, which then leads to decreased heart rate, decreased vascular resistance, and eventually syncope (4). This is the disorder which we will examine in our study.

Traditionally, head-up tilting has been used as a model for orthostatic stress, in that the patient is tilted from a supine to a standing position and then remains standing for a specified time period (usually from 20-60 minutes). Patients that experience syncope during this procedure are usually given a diagnosis of orthostatic intolerance. Patients not prone to this disorder can be expected to be asymptomatic during the period of tilting and thus have a negative (normal) tilt-table test.

While the tilt-table test is of widespread use in the evaluation of syncope, there is a significant drawback to using this test in that there is a low incidence of symptomatic hypotension, and thus positive tilt-table tests (5). In healthy subjects, the incidence of positive tests is usually very low, and one study by Hainsworth and Al-Shamma reported no positive tests in 66 healthy subjects when tilted to 60 degrees for 20 minutes (6). As a result, these subjects are producing no data with which to evaluate their predisposition to syncope, and the study loses power by not having data for these subjects. Furthermore,

even those patients that appear predisposed to orthostatic intolerance by history and physical (i.e. prodrome of syncope when standing followed by loss of consciousness, orthostatic hypotension, etc.) often have negative tilt table tests, implying that the sensitivity of the test is below acceptable standards. In another study by Wahba *et. al.* only 2 of 67 patients experienced syncope when subjected to the above tilt table test, and even after prolonging the test to 1 hour only 19% of patients were positive (7). A continuous variable system is needed to evaluate syncope in which a significant percentage of patients experience symptoms and hence provide data for comparison to other subjects.

A method that has been used to measure orthostatic tolerance that avoids the major drawback outlined above is lower body negative pressure (LBNP). In this method, the patient is placed into a LBNP chamber and subjected to various degrees of negative pressure in their lower extremities, usually ranging from –20 mmHg to –60 mmHg. This negative pressure provides a pressure gradient and thus a force for venous pooling in the extremities. As a result, similar to head-up tilting, it provides a model for orthostatic stress. However, if it could be combined with tilt-table testing, it appears to offer multiple advantages over tilt-table testing alone. The main advantage is that all subjects can be induced to syncope in this method, as it provides a more severe orthostatic stress. In doing so, it converts the binary variable data produced during tilt-table testing (syncope vs. no syncope) into a continuous variable that is "time to syncope," whereby it can be assumed that those individuals *less* prone to syncope will have a *greater* time to syncope when exposed to negative pressure. This offers a significant advantage in data analysis over tilt-table testing because the data from all subjects can be analyzed and will differ from one another, such that all subjects can be put on a gradient based on their time to syncope. In this manner, LBNP plus tilt-table testing is a much more sensitive test than tilt-table testing alone, and all subjects have unique data that can be compared to other subjects. Hainsworth and El-Bedawi published a series of two small studies in 1994 examining this method both in normal subjects and syncopal patients which demonstrated intra-individual reproducibility (5,8). It is therefore not necessary to test reproducibility of the method in our study, but rather we will expand on previous studies by using LBNP plus tilt-table testing to assess various drug compounds and subgroups of the population.

In this manner, we will test the hypothesis that in those patients previously diagnosed with vasovagal syncope, midodrine will increase the time to syncope to that of normal healthy subjects. Midodrine is an antihypotensive and alpha-sympathomimetic agent that has been shown in previous randomized, multi-center, double-blind, placebo-controlled studies to have efficacy in improving standing systolic blood pressure and syncopal symptoms (9,10,11,12). It is FDA approved for orthostatic hypotension, and is currently undergoing phase IV trials to determine its effect on quality of life for this disorder. While midodrine has not yet been approved for vasovagal syncope, several studies, including one randomized and two non-randomized studies, have demonstrated efficacy in this regard (13,14,15). Our study with midodrine will serve as an adjunct to other studies in providing evidence of midodrine's efficacy in vasovagal syncope, as well as to provide additional evidence that, not only is our method reproducible, but that it can be used to evaluate any given therapy for syncope, as well as to measure the tendency to syncope of any individual in the population. Therefore, after midodrine has been tested in this manner, we will expand on this method by testing a number of drug compounds to assess drug efficacy in orthostatic tolerance, and will also test various subgroups previously thought to be more prone to syncope more than the general population (i.e. athletes, women in various phases of the menstrual cycle, elderly patients, etc.).

a. Hypothesis

1. Patients with vasovagal syncope will increase their time to syncope to that of normal subjects after the administration of midodrine using LBNP plus tilt-table testing.

C. Methods

a. Power Calculation

As stated above, LBNP plus tilt-table testing has previously been assessed in two studies by Hainsworth and El-Bedawi, done eight years ago and examining the differences in time to syncope both

between normal subjects of different ages and gender (5) and in normal subjects versus those with unexplained syncope (8). We will use the latter study for our calculations of power size (8), as we hypothesize that midodrine will lengthen the time to syncope in those with orthostatic tolerance to that of normal subjects. In that study, Hainsworth and El-Bedawi determined that the time to induce syncope in 50% of the subjects from each group differed by 7.5 minutes. We will set our clinical effect to 75% of that found in the Hainsworth study (8), or a difference in median time to syncope of 5.6 minutes, because this is still a significant clinical effect despite the fact that it does not fully compensate for the difference observed in the Hainsworth study (we do not want to underpower the study by setting our clinical effect at exactly that observed in the Hainsworth study). Using the standard deviation estimated by the data given in the Hainsworth study of 4.5, we will need 8 subjects to perform the study, given that it is a crossover study and thus all patients will receive both midodrine and the placebo.

b. Patient Selection

We will study 8-15 subjects (assuming drop-out, etc.) with previously diagnosed vasovagal syncope (either clinically or through a positive tilt-table test). All patients will be over 18 years of age and will be recruited from the staff at Columbian Presbyterian Medical Center and/or from the general population. Members of the research team will approach potential subjects, explain the study, and obtain informed consent. A flier may be used if recruitment from around the medical center does not meet our enrollment goals.

D. Study Location

The study will take place in the Autonomic Function Laboratory of the Irving Center for Clinical Research, as well as in the tilt-table laboratory on the third floor of Harkness Pavilion.

E. Study Protocol.

The methods used in our experiment are based on those published by Hainsworth and El-Bedawi (5,8).

A rough diagram of the LBNP-tilt-table setup is shown below in Figure 1. It consists of the lower body negative pressure secured to approximately one half of a padded electric tilt-table, the angle of which is adjusted manually by holding down a button until the table reaches its desired angle, as displayed by a gauge on the side of the table. The subject is fitted into an airtight neoprene suit (made of the same material as that worn by kayakers/scuba divers) which covers the upper half of the body. After lying on the table, the subject is fitted with ECG electrodes, as well as a Colin 7000 monitor (a non-invasive device that determines blood pressure using a method by correlating sphygmomanometric measurements with a radial pulse waveform). The subject then slides into the LBNP chamber through a circular opening up to the iliac crest, and then straps are placed on the patient's upper body to prevent movement during tilt. The upper body portion of the patient's suit is then folded over a rim that surrounds the chamber's opening, so that the patient's lower body is immersed in the chamber and an airtight seal has been formed within the chamber (as air cannot enter or escape the chamber). The chamber is turned on, and negative pressure is generated through the pipe of a commercial vacuum cleaner. The chamber is fitted with a gauge to indicate the pressure below atmosphere. The level of the subatmospheric pressure is controlled by use of a variable transformer controlling the vacuum pump motor.

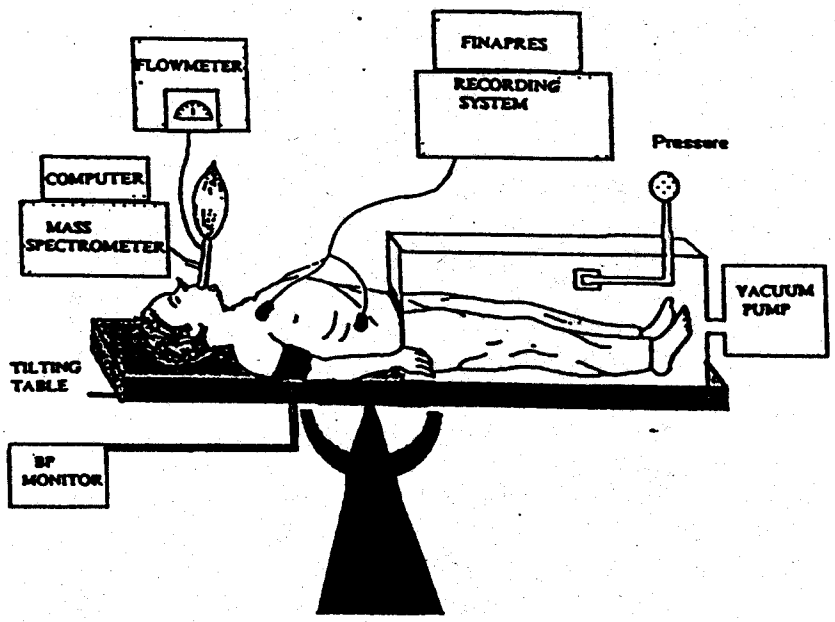

Figure 1. Schematic diagram of the tilt-table with lower body negative pressure, from Hainsworth and El-Bedawi, Clinical Autonomic Research, 1994 (5).

After being secured and immersed in the chamber, the subject remains supine for 20 minutes. They are then tilted head-up by 60 degrees for 20 minutes (phase 1). Then, while still in this position, a subatmospheric pressure of –20 mmHg is applied to the lower body for 10 minutes (phase 2), –40 mmHg for 10 minutes (phase 3), and –60 mmHg until the subject undergoes either syncope or presyncope. Presyncope encompasses symptoms that precede a syncopal episode, specifically dizziness without vertigo, nausea, lightheadedness, a feeling of warmth, or diaphoresis, that will be equivalent to syncope in our study. The test is terminated by stopping the suction and returning the subject to the supine position when they experience either syncope or presyncope during any one of the above phases. At this time, the time to syncope is recorded in relation to the beginning of phase 1 (after the 20 minute resting period at the beginning of the study). The subject can also terminate the test at any time on their own. When the subject feels as if he or she has returned back to baseline, they are unstrapped, exit the LBNP chamber, and are allowed to rise to the sitting position. If the subject is still asymptomatic, the ECG and Colin 7000 devices are removed and the patient can then rise to the standing position, with assistance. If no symptoms arise during this time, the subject can walk with assistance, and then on their own if they feel steady, at which point they are permitted to leave.

Subjects will participate in the protocol two times. During the two visits, the patients will be randomized to midodrine (5 mg) and a placebo. The patient will receive one of the two therapies during the first visit, and then will cross over to receive the other therapy during the second visit. Both the investigators and the subjects will be blinded to the therapy. After the subject is given treatment (either midodrine or placebo), they will wait one hour to allow the treatment to take effect (the half life of midodrine is approximately one hour) and then undergo the protocol. They will then return to the center at least 7 days after the first visit and participate in the protocol again, this time with the alternate therapy. Midodrine is expected to lengthen the baseline time to syncope by approximately 7.5 minutes in relation to placebo, although we have powered our study such that a lower effect can be detected.

a. Measures

The time to syncope will be measured in relation to the start of phase 1 (i.e. if syncope or presyncope occur 20 minutes after the start of phase 1, the time to syncope is 20 minutes).

b. Analyses

The primary analysis of this study is comparing median change in time to syncope with midodrine when compared to placebo. A paired t-test will be done to assess the hypothesis that median time to syncope is significantly different when patients are given midodrine as compared to placebo.

F. Safety and Precautions

The main risk of the study pertains to the administration of midodrine. In previous clinical trials, the most frequently reported adverse reactions were supine hypertension and pruritus. Less frequent reactions included nausea/vomiting, pilo-erection, dysuria, urinary retention, urinary frequence, and weakness/fatigue (16). However, midodrine has been marketed in several countries worldwide and has an excellent safety record. Previous studies examined the adverse events associated with taking midodrine over time. We will only be administering the drug one time in our study, at a low dose, and a physician will be present to monitor adverse events at all times. If the Investigator deems an adverse event to be excessive, the study will be stopped in that subject.

During the study protocol, all subjects will have their blood pressure and heart rate measured continuously. The induction of syncope in itself has never been shown to be harmful to patients. Consciousness is restored within seconds of being returned to the horizontal position. Full precautions are also taken throughout the study to ensure that no trauma is experienced during the syncopal event (the patient is placed on a padded table and strapped down) or after the syncopal event occurs (with maximal time and assistance given for the subject to fully recover after their syncopal event before leaving the hospital).

G. Benefits

There are no direct benefits to the patient.

H. Inclusion Criteria

Patients must fulfill the following criteria for inclusion into the study: (1) the patient is 18 years of age or older, (2) the patient has been previously diagnosed with vasovagal syncope, either clinically or with a previous tilt-table test

I. Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria: (1) the patient has a history of supine hypertension greater than 180/110 mmHg, (2) the patient has a history of, or is currently receiving midodrine therapy, (3) the patient has a history of an adverse event to midodrine, (4) the patient is a pregnant or lactating female.

Appendix I: Specific IRB Information

J. Confidentiality

Any information obtained during the study and identified with the patient will remain confidential

K. Study Location

The study will take place in the Autonomic Function Laboratory of the Irving Center for Clinical Research.

L. Alternatives to Participation in this Study

The alternative to participating in this study is not to participate in this study.

M. Compensation

Subjects completing the study will receive $100 compensation.

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