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Rationale for the Prevention of Syncope Trial IV: Assessment of Midodrine

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Abstract

Background—Vasovagal syncope is a common problem associated with a poor quality of life, which improves when the frequency of syncope is reduced. Effective pharmacological therapies for vasovagal syncope have been elusive. Midodrine is a pro-drug whose primary metabolite is an alpha-1 adrenoceptor agonist. Small studies have suggested that it may be beneficial in syncope, but all have had significant methodological limitations. A placebo-controlled clinical trial of midodrine for the prevention of vasovagal syncope is needed.

Structure of study—The Prevention of Syncope Trial IV (POST 4) is a multicenter, international, randomized, placebo-controlled study of midodrine in the prevention of vasovagal syncope. The primary endpoint is the time to first recurrence of syncope. Patients will be randomized 1:1 to receive midodrine 10–30 mg/day or matching placebo, and followed for 1 year. Secondary endpoints include syncope frequency, presyncope, and quality of life. Primary analysis will be performed with an intention to treat approach, with a secondary on-treatment analysis.

Power calculations—A total sample size of 112, split equally between the two groups achieves 85% power to detect a 50% relative risk reduction when the event rates are 55% and 27.5% in the placebo and midodrine arms. Allowing for 20% dropout, we propose to enroll 140 patients.

Registration—POST 4 is registered with www.clinicaltrials.gov (NCT01456481).

Implications—This study will be the first adequately powered trial to determine whether midodrine is effective in preventing vasovagal syncope. If it is effective, then midodrine may become the first line pharmacological therapy for this condition.

Keywords

vasovagal syncope; randomized clinical trial; quality of life

INTRODUCTION

Vasovagal syncope is a common and frequently distressing problem. About 40% of people faint at least once in their life, and at least 20% of adults faint recurrently [3;21]. Up to 0.9% of primary care visits are for syncope and most are for vasovagal syncope [11]. There is an early peak incidence around 15 years for young women and a later significant rise in visits

for both sexes over age 65 years. The proportion of emergency room visits due to syncope is about 1%. In the United States about \$2.4 billion is spent yearly in hospitals on syncope [29].

Midodrine Hydrochloride to Treat Vasovagal Syncope

Midodrine is a pro-drug whose active metabolite is an agonist of the peripheral alpha-1 adrenergic receptor [14;32;33], without penetration of the blood-brain barrier. It causes both venoconstriction and arteriolar constriction, thereby increasing cardiac output and increasing peripheral resistance [14;32;33]. Midodrine is rapidly converted into the active metabolite and the pharmacokinetic and pharmacodynamic half-life of the metabolite is about 2.5 hours, which necessitates multiple daily dosing [5]. The drug is well tolerated, with dose-related and easily reversible side effects including supine hypertension, nausea, scalp paresthesias, piloerection, urinary retention, and rash.

Numerous early studies suggested that the hypotension accompanying vasovagal syncope is due to an abrupt withdrawal of sympathetic traffic, resulting in vasodilatation and a reduction in peripheral resistance [8–10]. More recently, we [7] and others [28;30] have reported that the principle hemodynamic change leading up to presyncope on tilt tests was peripheral venous pooling, implying a reduction in venous return. Therefore the hypotension of vasovagal syncope might be due to a failure of venoconstriction, vasoconstriction or both. Alpha-1 adrenergic agonists could address both mechanisms. While etilefrine was completely ineffective in a multinational European placebo-controlled trial [17], **midodrine** showed promise in 4 prospective controlled studies of midodrine in vasovagal syncope, although none were adequately designed. Kaufman et al. [4] studied midodrine with tilt test outcomes, which are known not to predict clinical outcomes. Ward et al. [31] studied only the most extremely symptomatic patients, and only for one month. Qingyou et al. [15] studied children in a protocol driven by tilt test outcome, with a potential expectation bias, and was contaminated with fludrocortisone as therapy. Finally, Perez-Lugones et al. [13] was open label, and there is a very strong possibility of placebo effect in syncope clinical trials [1;2;12;26]. Despite the significant methodological flaws the reports suggest absolute and relative risk reductions in these highly symptomatic populations of about 63% and 70% respectively. Recently, Romme et al. [18] reported a more modest relative risk reduction of 26% in a placebo controlled crossover study of midodrine 5mg BID for 3 months per phase. The Romme study selected a “refractory” population (who failed a lead-in physical countermeasures phase), and looked at outcome that included presyncope (in their primary outcome measure) over only 3 months per intervention. Their data may reflect either true midodrine inefficacy, may be specific to their design issues, or reflect differences in their patient selection. If one pools all 5 trials of midodrine for vasovagal syncope together (despite their methodological differences), they show a weighted mean relative risk reduction of 62% in the recurrence of syncope.

We therefore propose a prospective, randomized, placebo-controlled study of midodrine in the prevention of syncope in patients with moderate-to-severely frequent syncope. The diagnostic inclusion criteria will be based on the Calgary Syncope Symptom Score [25], and the primary outcome will be syncope recurrence.

STUDY AIM

The primary hypothesis is that in patients at moderate-to-high risk for recurrences of vasovagal syncope, a decision to treat with midodrine will increase the time to the first recurrence of syncope compared to placebo. The primary endpoint is the first syncope recurrence. The major secondary hypotheses are that midodrine will reduce the frequency of

recurrent syncopal spells and the frequency, duration, and severity of presyncopal spells; and that it will improve quality of life.

STUDY DESIGN

The Prevention of Syncope Trial IV (POST 4) is a longitudinal, prospective, parallel design, two-arm, placebo-controlled randomized clinical trial that will begin in 2012. Patient enrollment will conclude in 2015 and follow-up and data analysis will conclude in 2017. Overall study flow is shown in Figure 1. The POST4 study will follow patients for a full year in a parallel group design, use only syncope in the primary endpoint and will force a dose titration as tolerated. We anticipate that these study design features will result in a baseline outcome rate similar that observed in POST 2 [16] and provide a reasonable estimate of the true clinical effect of midodrine.

Patients are eligible if they are age ≥ 18 years, have a score of ≤ 2 on the Calgary Syncope Symptom Score for Structurally Normal Hearts, and ≥ 2 syncopal spells in the year preceding to enrollment. We observed in POST2 [16] that patients with a history of at least 2 syncopal spells in the year before assessment have a probability of syncope in the next year of 55% (unpublished observation). These criteria define a syncope population that many physicians might attempt to treat.

Patients will be excluded if they have other causes of syncope, cannot give informed consent, have important non-cardiovascular or cardiovascular diseases or a permanent pacemaker, glaucoma, hepatic or renal disease, urinary retention, a seizure disorder or hypertension (blood pressure ≥ 140/90 on 2 occasions). Patients will also be excluded if, during a 5 minute stand test, they have postural tachycardia (heart rate increase >30 beats per minute) or orthostatic hypotension (systolic blood pressure decrease >20 mmHg). Each center will complete a screening log of eligible but non-randomized patients that will contain demographic data and the reason for non-randomization. These patients will not be followed within the study.

Study procedures will follow the principles outlined for human experimentation in the Declaration of Helsinki. Each study site will obtain study approval through their Institutional Review Board. All patients will provide signed informed consent prior to participation in this study.

Rationale for Syncope Symptom Score inclusion criteria

The Calgary Syncope Symptom Score (CSSS) is used to diagnose vasovagal syncope in patients with structurally normal hearts [25]. It has an overall 90% accuracy in distinguishing vasovagal syncope from other causes of syncope in this population, and this is higher in patients under 60 years of age. It provided the diagnostic inclusion criteria for POST2 [16], and for a study of the impact of a parental history of fainting on the likelihood of fainting in offspring [21]. The use of this score will provide a validated, quantitative, objective, diagnostic inclusion criterion that, by obviating the need for head-up tilt testing, will provide for rapid translation of the clinical trial results into community practice.

Randomization and Study Arms

Patients will be allocated randomly and equally in a double-blinded fashion to receive midodrine 5mg three times a day, 4 hours apart during daytime hours (nominally 8am, noon, 4pm), or a placebo. Patients will receive either active treatment or placebo for 1 year. The reason for the exposure to treatment of 1 year is to minimize observation bias for the secondary objectives. Randomization will be performed centrally in permuted blocks of 2, 4, and 6 for different sites using central computer-generated lists of random numbers. The

randomization will be performed centrally with the unblinding key only at the coordinating center. The local PI and study coordinator, in addition to the patient, will be blind to allocation throughout the duration of the study.

Forced Dose Titration

Patients will be incremented or decremented as necessary or tolerated over 2 weeks to a final dose of 2.5 – 10 mg tid q4h or matching placebo, and if necessary 2.5 – 5 mg bid q6h. The top dose will be encouraged (forced titration up except for cause) and will not be exceeded. The primary guide to dose adjustment will be patient tolerance and anticipated compliance. If intolerable symptoms persist, the medication will be discontinued and the patient released from the study. Study dropouts will be included in the intention to treatment analysis, and censored at the time of dropout.

Assessment of Blinding

Blinding may prove challenging due to common midodrine side effects including supine hypertension, scalp paresthesias, piloerection, although side effects were more frequent with placebo than midodrine in a recent study [18]. The effectiveness of blinding will be assessed at the end of the study by asking both the patient and the site study coordinator to guess the randomized therapy, and comparing the correct responses to the expected rate of 50%.

Other Treatments During Study

All patients in both groups received standard of care for patients with vasovagal syncope. These included advice on high sodium/high fluid volume diet and training in postural maneuvers to prevent fainting in a standardized prescribed manner using written instruction sheets. Patients will be discouraged from receiving permanent pacemakers, beta-blockers, other alpha-adrenergic agonists or antagonists, antidepressants, scopolamine, theophylline, or fludrocortisone until after the primary outcome event. Use of non-study medications will be recorded and compared retrospectively.

Follow-up

Patients will complete a diary of presyncopal and syncopal spells daily, as has been used in prior syncope trials [22]. Study nurse coordinators will see the patients every 3 months for 12 months and be supplied with study drugs at those times. Patients will be asked to notify the study nurse if they experience a syncopal spell between clinic visits and will be interviewed by the syncope clinic within one week of the date of the spell. Compliance will be assessed by pill count.

DATA ANALYSIS

The primary outcome measure is the time to the first recurrence of syncope. It provides for an outcome without requiring that patients persist in a study they feel has not helped them. The time to the first recurrence of syncope has been shown to correlate very well with the frequency of syncope over a several year follow-up [6], and the frequency of syncope in turn correlates with the diminution of quality of life in patients with this disorder [20]. The verification of syncope will be done by recording the nature of the syncopal spell, by collateral history from bystander witnesses, and by examination of the patient for signs of physical trauma such as abrasions, contusions, and fractures. Patients are instructed to contact the clinic within 1 week of a syncopal spell and will be interviewed in the clinic.

The primary analysis will be on an intention-to-treat basis. Patients who discontinue their allocated treatment, drop out of the study or are withdrawn by their physician for reasons related to the treatment will be considered treatment failures at that time. Patients who drop

out of the study or whom their physician withdraws for reasons unrelated to the treatment and who have not experienced a syncopal episode will be censored at that time for a secondary on-treatment analysis. A subsequent efficacy analysis will be done on those patients who complete the course of treatment at least until their first syncopal spell. The analytic approach for both the intention-to-treat and efficacy analysis will use the Kaplan-Meier method, and the difference between the curves will be assessed using a Mantel-Haenszel test. Cox proportional hazards modeling will be used to examine the treatment effect. These two approaches should provide for a better estimate of the reduction in the risk of syncope, than using either approach alone.

Presyncope frequency, duration, and intensity will be secondary outcome measures. Patients will complete the Calgary Presyncope Scale daily. This is a Likert-like scale that captures presyncope frequency, duration, and intensity that was used in the Prevention of Syncope Trial to capture this important outcome measure [27]. *Quality of life* will be compared in treated and untreated patients. Each patient will complete the Euroqol EQ5D and the ISQL [19] at baseline, and 6 months. These forms have been completed by over 300 syncope patients in Calgary and all POST subjects and respond to the frequency of syncopal spells [20] and to the improvement in clinical status that accompanies open label permanent pacing [23]. Adverse events in both the midodrine and placebo groups will be carefully tracked throughout the study. Cost-effectiveness analyses are planned to determine whether any benefits from midodrine therapy might be viable in this era of limited healthcare resources.

Data analysis will use mixed models repeated measures, which allows for optimal utilization of data even in the presence of missing data. If the underlying normality assumptions are violated appropriate transformations or nonparametric analyses will be used. Analysis will be done on an intention-to-treat basis using the last observation carried forward approach.

We will assess whether clinical variables predict recurrence of syncope both with and without midodrine therapy. The variables to be tested include age; sex; number, duration, and frequency of historical syncopal spells; baseline supine heart rate and blood pressure. The data will be analyzed as described above. A post hoc regression model will be developed which will examine potential interactions of these variables with midodrine therapy. We recognize that the study will not be adequately powered for this secondary analysis. Data could be pooled with that from the POST [22] and POST2 [16] studies to model predictors of syncope and response to pharmacological therapies.

Sample Size & Power Calculations

The study will be powered to address the primary hypothesis, that a decision to treat patients with midodrine will decrease the proportion of patients with syncope compared to treatment with placebo over time. The published data suggest a weighted relative risk reduction of 62%. A Clinically Significant Minimal Difference would be a more conservative 50% relative risk reduction in the proportion of patients with a syncope recurrence from 55% to 27.5%. The sample size calculations are based on the primary intention-to-treat analysis. This event rate in the placebo group is based on baseline characteristics and outcome rates in POST 2, in which a very similar patient population was studied. All patients had uniform, structured teaching on diet, hydration, and physical counterpressure manoeuvres, as they will in this study. These projected outcomes, therefore, are based on real, quantitative experience using conventional non-pharmacologic treatments. The primary intention to treat analysis will use the time to the first syncopal spell (TFS) as the outcome measure. The sample size calculations were done using Rollin Brant UBC calculator for independent proportions [24]. A total sample size of 112, split equally between the two groups achieves 85% power to detect a 50% relative risk reduction when the event rates are 55% and 27.5% in the placebo and midodrine arms, at a significance level $\alpha=0.05$ using a two-sided test.

One interim analysis will be conducted six months after half of the patients have been recruited. The use of the O'Brien-Fleming spending function will ensure that the study is terminated early only if there is an extreme difference between the two treatment groups ($p=0.0148$). The final analysis will be conducted at $p=0.0455$ with an overall alpha of 0.05. Loss of patients before the first syncopal spell will increase the necessary sample size. We anticipate a 25% drop out before a primary outcome (loss to follow-up for unknown reasons, loss to follow-up for reasons totally unrelated to syncope symptoms or treatment [e.g. pregnancy]), resulting in censored observations in the survival analysis. A dilution effect may also arise from patients whose compliance is poor. We therefore plan to increase the sample size to 112×1.25 , or 140 patients, 70 in each arm.

The actual event rates will be assessed at the time of DSMB interim review. The sample size might be adjusted at that time based on actual and projected event rates.

Patients will be classified as treatment failures if they experience at least one syncopal spell within the 12-month observation period, withdraw from the study due to intolerable side effects before the first syncopal spell or crossover to open label treatment before the first syncopal spell. Patient will remain in the group to which they are randomized for this analysis. Patients who are otherwise lost to follow-up (e.g. relocation) or who withdraw from the study for reasons unrelated to either symptoms or treatment will be censored at the time of last observation.

STUDY REGISTRATION

The *Prevention of Syncope Trial IV (POST 4): Assessment of Midodrine in the Prevention of Vasovagal Syncope* is registered with the National Institutes of Health sponsored ClinicalTrials.gov (www.clinicaltrials.gov) having study number NCT01456481.

STUDY ORGANIZATION

The Principal Investigator will be Dr. Robert Sheldon; the statistician will be Dr. Peter Faris; and the economist will be Dr. Brandon Manns (all of the University of Calgary). The Executive Committee will consist of Drs. Sheldon, Faris, Satish Raj (Vanderbilt University, Nashville, USA), Andrew Krahn (University of Western Ontario, London, Canada), Carlos Morillo (McMaster University, Hamilton, Canada), and Teresa Kus (University of Montreal, Montreal, Canada). An Outcomes Adjudication Committee will include selected investigators. Coordination, data management, and analysis will be performed at the University of Calgary. A Data Safety and Monitoring Committee will be recruited under the Chair of Dr. David Johnstone (University of Alberta, Edmonton, Canada).

Study sites have committed to participate in POST IV from Canada, United States, South America and Europe. Based upon participation in the POST2 study, we estimate that there will be 12–15 study sites.

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POST 4: Study Flow Diagram

Figure 1.
Study Flow diagram for the POST4 study. CSSS – Calgary Syncope Symptom Score.