Midodrine for the Treatment of Refractory Hypotension

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STUDY PROTOCOL

PURPOSE

We hypothesise that midodrine treatment of refractory hypotension in patients otherwise ready for discharge from the ICU shortens duration of receiving IV vasopressors and ICU length of stay without increasing hospital length of stay or putting the patient at risk of being readmitted to an ICU.

SIGNIFICANCE AND BACKGROUND

Midodrine is an orally available alpha-1 agonist, which is currently FDA approved for the treatment of symptomatic orthostatic hypotension. This indication is generally reserved for patients with chronic orthostatic hypotension that significantly impairs their daily activities of living despite standard care because midodrine carries the risk of supine hypertension. However, in patients without orthostatic hypotension, this adverse reaction is theoretically less prevalent due to preserved baroreflex buffering that maintains blood pressure homeostasis.[1] Midodrine has several unique pharmacological properties compared to other medications in its class: it exerts significantly less gastrointestinal effects, has minimal central nervous system side effects, and demonstrates excellent bioavailability following oral administration.[2] These desirable pharmacological properties lead to midodrine's potential application for new indications.

One of the most frequently prescribed off-label indications for midodrine is prevention of intradialytic hypotension. A systematic review was conducted evaluating the use of midodrine for the prevention of intradialytic hypotension.[3] 56 patients received a one-time dose of 2.5 to 10 mg of midodrine 15–30 minutes prior to each dialysis session compared to a placebo-control group. The midodrine group's mean pre- and post- dialysis systolic blood pressure (SBP) was 128.1 (90.5–138.7) mmHg and 115.5 (81.5–129.9) mmHg and pre- and post-dialysis diastolic blood pressure (DBP) was 72.4 (55.4–81.4) mmHg and 58.9 (50.2–72.5) mmHg. The control group's mean pre- and post-dialysis SBP was 123.2 (73–135.2) mmHg and 103.1 (64.9–116.5) mmHg and pre- and post-dialysis DBP was 58.1 (44–76.2) mmHg and 52.5 (32.6–66.8) mmHg. The midodrine group demonstrated a statistically significant greater post dialysis and nadir SBP with a mean difference of 12.4 mmHg (7.1–17.7; $p<0.0001$) and 13.3 mmHg (8.6–18; $p<0.0001$) and post dialysis and nadir DBP with a mean difference of 7.3 mmHg (3.7–10.9; $p=0.0001$) and 5.9 mmHg (2.7–9.1; $p=0.0004$) vs. the placebo control group.[3]

Although frequently prescribed as an off-label indication, the optimal dosing range for midodrine in the treatment of hypotension unrelated to orthostasis has yet to be fully determined. Our proposed study will use the maximum dose that has been previously shown to have a strong correlation with effect on systolic blood pressure. This dosing is based on a recently published randomised, two-centre, double-blind, four-way complete crossover, single dose study in patients with neurogenic orthostatic hypotension. This study demonstrated that there was a linear relationship between dose and change in systolic blood pressure when administering a single dose of midodrine from 2.5 mg to 20 mg. These doses also produced a predictable blood pressure response and blood concentrations. The time to maximum concentration of midodrine was 15 to 30 minutes with an elimination half-life equal to 30 minutes, and active metabolite, dysglymidodrine, equal to 4 hours.[4] There are limited efficacy and safety data supporting off-label use. Based on billing records, a total of 6,443 patients were prescribed midodrine as an inpatient at MGH since 1998. Utilisation of midodrine has steadily increased over the last decade with 1,200 patients being prescribed in 2010. Given that midodrine is only indicated to treat rare diseases, it is likely that the majority of these patients were prescribed midodrine as an off-label indication.

The only information available for off-label treatment of hypotension unrelated to orthostatic dysregulation is based on observational data. Midodrine was successfully used as an alternative to intravenous vasopressors in the treatment of hypotension related to carotid artery stenting. Eleven patients received intravenous dopamine infusion in an intensive care setting whereas 4 patients received midodrine in a regular telemetry floor to treat hypotension. The cost of hospitalisation was significantly higher in the dopamine group due to the need for ICU admission and no major side effects were noted in either group.[5] In another study, midodrine was used as an alternative to intravenous inotropic therapy in patients with hypotension associated with stunned myocardium. The authors concluded that midodrine can shorten the duration of intensive care unit and hospital stay in this setting.[6] At MGH's ICUs,

midodrine has been observed to effectively wean patients off continuous IV vasopressors. For patients whose only barrier to discharge from the ICU was administration of continuous medications, midodrine also appeared to decrease ICU length of stay. However, it is unknown if midodrine shortened their total hospital LOS or put the patient at risk of being readmitted back to an ICU. Additionally, midodrine appears to be well tolerated by patients when prescribed at MGH because there have been no safety reports submitted due to an adverse reaction.

No previous studies have examined the use of midodrine for the treatment of hypotension in an ICU setting. We are investigating a new indication for midodrine as the treatment for hypotension in critically ill patients. We expect that midodrine will decrease the time of patients being administered continuous vasopressors by 6 hours and therefore accelerate their readiness for ICU discharge. This has potential to have a significant impact on healthcare costs by reducing ICU and hospital LOS.

DESCRIPTION OF RESEARCH PROTOCOL

Study Design
The study is a randomised, double-blind, placebo-controlled, multi-centric trial expected to enrol 120 subjects in order to detect an expected statistically significant difference of 6 hours (from initiation of drug until discontinuation of IV vasopressors) between the two groups.

Subjects are being enrolled at:

1. Massachusetts General Hospital, Boston (MGH)
    - Local IRB: Partners Human Research Committee, protocol number: 2016P002045
2. Sir Charles Gairdner Hospital, Australia (SCGH)
    - Local IRB: Sir Charles Gairdner Hospital HREC, protocol Number: 2015-098
3. Beth Israel Deaconess Medical Center, Boston (BIDMC)
    - Local IRB: Committee on Clinical Investigations, protocol number: 2018P000162

Recruitment
Subjects will be identified from the ICU census on a daily basis by study personnel and identified by other ICU clinicians. If identified subjects meet inclusion/exclusion criteria they will then be approached by a specialised health care provider. The specialised health care provider will be a physician that is part of the clinical staff in the ICU who has first-hand knowledge of the subject's medical history. This physician will approach potentially eligible subjects to introduce them to the research study. If both the specialised health care provider approves his or her subject to be contacted for research purposes and the subject agrees to be contacted by study staff discussed verbally during the course of providing medical care, a study physician will then approach the subject to obtain informed consent.

Subject Selection
Inclusion criteria:

- At least 18 years of age
- Admitted to the intensive care services at MGH, SCGH, or BIDMC
- Requiring IV vasopressors at a rate of less than 100 mcg/min of phenylephrine, or 8 mcg/min of norepinephrine, or metaraminol 60mcg/min and unable to wean for more than 24 hours while still maintaining desired blood pressure goals.

Exclusion criteria:

- Clinical evidence of inadequate tissue oxygenation
- Clinical evidence of liver failure
- Hypovolemic shock or hypotension due to adrenal insufficiency (based on clinical suspicion or available routine testing)
- Pregnancy confirmed with a pregnancy test. Women between the ages of 18–55 who have not had a surgical hysterectomy will only be eligible for inclusion if they have a negative urine pregnancy test. Pregnancy testing will not need to be repeated if there is a documented negative urine pregnancy test that was obtained within 7 days prior to starting study drug, provided the woman was an ICU inpatient throughout that period of time.

- Chronic renal failure (serum creatinine >2mg/dL or 180 µmol/L)
- Severe organic heart disease (ejection fraction less than 30%)
- Acute urinary retention
- Pheochromocytoma (based on clinical suspicion)
- Thyrotoxicosis (based on clinical suspicion)
- Enrolment in another clinical trial
- Midodrine as pre-admission medication
- Any known allergies to midodrine
- Bradycardia (HR <50/min)
- No enteral route available

Consent

Informed consent will be obtained from the participant by a study physician. If the subject lacks mental competency based on the mini mental status exam to provide informed consent, the subject's designated surrogate will be explained their responsibility as a LAR to make decisions on the patient's behalf, and will be asked to provide consent. The LAR will also be explained that should the participant re-gain mental capacity, he/she will be formally consented. As part of this, the study physician will address the patient explaining what procedures have been held so far, the purpose, risks and benefits of the study. The study physician will then explain the patient's right to decide as to whether they wish to continue being a participant in the study. Based on the patient's decision, study procedures will be continued or withheld immediately. The following categories of surrogates (listed in general order of preference) may provide consent in writing on behalf of potential subjects incapable of providing informed consent:

- Health Care Proxy, a court appointed guardian of the person with specific authority to consent to participation in the research study, but also next-of-kin in the following order of priority unless otherwise specified by law: spouse, adult child (18 years of age or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older).

Assent of subjects is required for participation in the research unless the subject is incapable of giving assent due to his/her medical condition. If the individual objects to participation, s/he will not be enrolled. The Investigator will document the relationship of the surrogate to the subject in the research record.

Study Procedures

Prior to randomisation, if subjects are eligible based on inclusion/exclusion criteria, informed consent will be obtained from participants. Once informed consent is obtained, the following information will be collected from the subject's medical record: demographics, past medical/surgical history, preadmission medication list, severity of illness at time of admission, blood pressure, aspartate aminotransferase, alanine aminotransferase creatinine, troponin, cortisol level.

The study drug or placebo will be selected based on the randomisation scheme and prepared by investigational pharmacists. All study personnel will be blinded, except the investigational pharmacist, to the treatment group of the subject. Subjects will be randomised to receive either 20 mg PO every 8 hours of midodrine, or placebo PO every 8 hours.

The study drug will be delivered in a double-blinded manner until:

- ICU discharge
- Rate of phenylephrine exceeds 100 mcg/min, or rate of norepinephrine exceeds 8 mcg/min, or rate of metaraminol exceeds 60mcg/min
- Subject exhibits signs and symptoms of organ failure or hypoperfusion
- Serious allergic adverse event related to midodrine
- Epinephrine requirement
- Death

If the blood pressure goal is met for more than 24 hours without IV vasopressors and the attending physician determines that the study drug is no longer required, the study drug may be discontinued at the discretion of the treating physician.

Outcomes
Study endpoints include the following:

- *Primary endpoint*:
  - Hours from initiation of midodrine until discontinuation of IV vasopressors
- *Secondary endpoints*:
  - ICU length of stay (LOS), hospital LOS, rates of ICU readmission
- *Safety endpoints*:
  - hypertension (increase in blood pressure to a systolic blood pressure (SBP) 20 percent higher than the predefined goal set by the primary team), bradycardia (decrease in heart rate 20 percent lower than the predefined goal set by the primary team), hemodynamically significant tachyarrhythmia (>20 percent decrease in systolic blood pressure).

Adverse Event Reporting
Our patient population is by definition critically ill in the ICU. It is expected that they will have a number of unrelated adverse health events (AE) during the course of their hospital stay. Therefore, we will limit the scope of our AE monitoring and recording to the following:

- Serious Adverse Events, defined as
  - Death, believed to be related to the study drug, or a death that is unexpected considering the acuity of a patient
  - A life-threatening experience believed to be related to the study drug
  - Persistent or significant disability or incapacity that is of greater frequency or severity than what would be normally expected in the course of critical illness
  - An event that jeopardises the Human Subject and may require medical or surgical treatment to prevent one of the preceding outcomes and is not expected in the course of critical illness
- Adverse Events possibly related to the study procedures are pre-specified in the list below:
  - Hypertension
  - Bradycardia
  - Hemodynamically significant tachyarrhythmia
  - New organ failure

Evidence for adverse events related to midodrine will be assessed until completion of all study measurements. They will also be included in the FDA Annual Progress Report.

Statistical Analysis
Please refer to the Statistical Analysis Plan (SAP).

POSSIBLE BENEFITS

We cannot guarantee any personal benefits from participating in this study. However, potential benefits to the subject may include shorter duration of receiving IV vasopressors, and shorter length of stay in the ICU and hospital. Earlier discharge from the ICU and hospital reduces the risk of developing nosocomial infections and reduces the total cost of the hospital admission. Information gathered from this study will help researchers determine if midodrine is safe and effective at decreasing duration of IV vasopressors and shortening ICU length of stay without increasing the risk of ICU readmission or increasing hospital length of stay.

POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

The very common side effects of midodrine reported in previous studies include pilomotor-like reactions, paraesthesia, pruritus, and dysuria. The most common side effects are headache, supine hypertension, flushing, rash, nausea, dyspepsia, stomatitis, chills, and pain. Less common side effects comprise sleep disorders, insomnia, restlessness, excitability, irritability, and reflex bradycardia. Rare side effects are tachycardia, palpitations, abnormal hepatic function, raised liver enzymes.

These reactions rarely resulted in discontinuation of medication. These side effects may make the subject uncomfortable but do not pose any immediate harm. The subject will be assessed daily by study personnel and all efforts will be made to minimise discomfort from these side effects. Other risks that the subject may be exposed to

as a result of midodrine include hypertension, bradycardia, and tachyarrhythmias.

Patients enrolled in the study will have the same safeguards as non-study patients in an ICU setting. For patients who have stable blood pressure and adequate tissue perfusion, midodrine has been used off-label frequently to treat hypotension in our ICU. Therefore, the risks and benefits of the study drug are similar to the risks and benefits of the current standard for treating this indication in ICU patients.

Midodrine is a pregnancy category C medication. Pregnant subjects will be excluded from the study because the exposure risks of midodrine to a developing fetus are unknown. Women between the ages of 18–55, who have not had a surgical hysterectomy, will only be eligible for inclusion if they have a negative urine pregnancy test. Pregnancy testing will not need to be repeated if there is a documented negative urine pregnancy test that was obtained within 7 days prior to starting study drug, provided the woman was an ICU inpatient throughout that period of time.

SUBJECT PROTECTION

Potential coercion of subjects will be avoided by obtaining informed consent by a physician who is involved in the study and is listed on the Research Staffing Form. Subjects or designated surrogate will have adequate time to decide to participate in the study. Fluctuation in a subject's mental competency is expected due to presence of sedatives or delirium. Therefore, if the subject's surrogate provides consent, a physician independent of the study will reassess the subject's mental competency using the MMSE once their Richmond Agitation Sedation Score returns to 0 or -1 or their Confusion Assessment Method for the ICU is negative. If the subject regains decision-making capacity, a study physician will obtain informed consent from the subject.

Privacy
The screening of patients, discussions with family/proxy/legally authorised representatives, and the consent process will occur in private settings with curtains/doors closed so as to provide privacy and comfort.

DATA SECURITY

Data Monitoring
The following areas will be reviewed by the monitor for completeness and accuracy: study binders, screening log, and eligibility adherence, consent forms, data retrieved from each patient during the study, adverse event reports, and pharmacy-related study contributions. Monitoring procedures will take place on-site, at close-out. A monitoring report will be completed to verify that the monitoring plan was followed. This will be presented to the lead PI and placed in the regulatory binder. This will also be included in the FDA Annual Progress Report to ensure compliance with the FDA Code of Federal Regulations Title 21, section 312, subpart D. A Data Safety Monitoring Board is in place, which will review the data collected, as well as adverse event reports and minor deviations logs.

Confidentiality and Security
General Protections: All study staff undergo ongoing training in proper research procedures, Good Clinical Practice, and the application of HIPAA privacy laws.

Data collection: Case report forms will be completed on site by study team members. Medical record numbers, names, dates or other identifiers will not be entered on REDCap. This platform will be used for storage and manipulation of all our de-identified data. For the different study centres, individual access groups will be formed and only the coordinating site will have access to all data.

Study file storage: All data obtained with subject identifiers will be kept in password-protected computer files behind the institutions' firewall. A crosswalk linking patient identifiers to study ID number will be maintained indefinitely by the principal investigator. Limited data will be retained on screened patients who do not meet entry criteria or who decline to participate. We will retain only the minimum data required to adequately summarise subject selection per CONSORT guidelines in the study publications. Paper records will be kept in locked filing cabinets within locked and secured offices to ensure confidentiality. All paper file contents will be shredded before disposal.

DISSEMINATION OF RESEARCH RESULTS

Patients will be thanked for their time throughout the study. There is no plan to share the data at the conclusion of the trial. Because study results are likely to be published a few years after a given subject's participation, it is not feasible to send subjects follow-up with the published results. The study investigators are concerned that mailing the published manuscript and an additional thank-you note years after participation risks violating subject privacy, as mailing addresses are increasingly likely to change with passing time.

STATISTICAL ANALYSIS PLAN

Study aims
This randomised, controlled clinical trial evaluates the effect of oral midodrine versus placebo on time to liberation from intravenous vasopressors in ICU patients with refractory hypotension. The aim of this study is to assess the effects of midodrine treatment in patients otherwise ready for discharge from the ICU. The primary hypothesis is that midodrine treatment shortens the duration of receiving IV vasopressors compared to placebo.

Study design
Prospective multi-centre randomised placebo-controlled trial.

Study population and study sites
The study will enrol patients admitted to an intensive care or high-dependency unit (ICU/HDU) and meeting all eligibility criteria detailed in the study protocol. Study sites include Massachusetts General Hospital (Boston, MA, USA), Sir Charles Gairdner Hospital (Perth, Australia), and Beth Israel Deaconess Medical Center (Boston, MA, USA).

Randomisation
Patients will be randomly allocated in a 1:1 ratio to receive either midodrine or placebo. Randomisation will be performed using a computer-generated randomisation list and will be stratified by study site. Randomisation lists will be created by an independent, unblended study team member, under the supervision of an independent statistician. The randomisation list will be provided directly to the research pharmacy, which will be responsible for preparing and dispensing the study medications following an active order for study medications. This includes preparation and blinding of the placebo in accordance with the study randomisation schema.

Study groups
1. Midodrine, 20 mg PO every 8 hours
2. Placebo (matched in appearance), PO every 8 hours

Outcomes
- *Primary endpoint*:
    - Time until discontinuation of IV vasopressors, measured in hours from initiation of midodrine until discontinuation of IV vasopressors
- *Secondary endpoints*:
    - Time to ICU discharge readiness, defined as the number of days from study drug initiation to meeting discharge criteria
    - ICU length of stay, defined as the number of days in the ICU prior to transfer to the general floor
    - Hospital length of stay, defined as the total number of days in the hospital after first study drug administration
    - Rates of ICU readmission, defined as the number of patients readmitted back to the ICU after prior discharge to the general floor
- *Safety endpoints*:
    - Hypertension (increase in blood pressure to a systolic blood pressure (SBP) 20 percent higher than the predefined goal set by the primary team), bradycardia (decrease in heart rate 20 percent lower than the predefined goal set by the primary team), hemodynamically significant tachyarrhythmia (>20 percent decrease in systolic blood pressure).

Data Collection
Baseline descriptive data collection will occur on day of enrolment and includes age, sex, ethnicity, APACHE II score, admission diagnosis, pre-existing co-morbidities (diabetes, coronary artery disease, asthma, peripheral vascular disease, renal failure, psychiatric disease, musculoskeletal disease, and others) obtained from the subject, the subject's family, and the subject's medical chart. Baseline laboratory data will be recorded (haemoglobin, white cell count, alanine aminotransferase (ALT), international normalised ratio (INR), bilirubin, urea, creatinine, troponin, lactate). During the study daily SOFA scores, blood pressure goals, total fluid balances, transfused red blood cell units, administered corticosteroids, use of epidural analgesia, vasopressor and study drug start and end

times will be recorded. Days between admission and discharge from the ICU and hospital will be recorded. Readmissions to the ICU during the hospital stay will be identified through daily medical record review.

Sample size estimation
The sample size estimation is informed by the previous observational study by Levine et al.[7] In this study, the rates of vasopressor administration decreased by 38% from −0.62 ± 1.40 mcg/min per hour to −2.20 ± 2.45 mcg/min per hour after addition of midodrine. Based on a median time of 17 h from midodrine initiation to discontinuation of IV vasopressors, the 38% reduction translates to an estimated 6 h difference. 6 h is also thought to be a meaningful time frame in terms of reduction in duration of vasopressor treatment. Accordingly, we expect that a sample size of 50 subjects per group will provide us with >80% probability (power) to detect a difference of 6 h in the primary outcome. Allowing for drop-out, our target sample size is 120.

Statistical analysis
The study analysis will be performed on a modified intention-to-treat basis: All patients who were randomised and received at least 1 dose of the study medication will be included in the analysis.

Baseline and demographic characteristics will be presented using descriptive statistics. Continuous data will be expressed as means and standard deviations, or medians and interquartile ranges (IQR), depending on variable distribution. The normality of variable distribution will be assessed by exploratory data analysis, including histograms and boxplots. Differences in continuous data between groups will be assessed using a parametric t-test or Mann-Whitney U test, as appropriate. Categorical data will be presented as frequencies and proportions and analysed using a Chi-square test. If expected cell counts are small (less than 5), Fisher's exact test will be used instead. For all analyses, a two-sided p-value of less than 0.05 will be considered statistically significant. All analyses will be conducted under the supervision of a statistician blinded to intervention group assignment. Experienced study staff will perform data analysis in collaboration with biostatisticians using statistical Stata version 13 (StataCorp LLC, College Station, TX) or later.

Analysis of primary and secondary outcomes
A parametric t-test or Mann-Whitney U test will be used, as appropriate, to determine whether time from initiation of midodrine until discontinuation of IV vasopressors, time from ICU admission to ICU discharge readiness, and ICU and hospital LOS differ between groups.

A Chi-Square or Fisher's exact test will be used to test whether rates of ICU readmission and incidence of adverse events are different between treatment groups.

Missing data
The frequency of missing values for each variable will be collected and reported as necessary. If there are missing values for the primary or secondary outcome variables, individual patients will be excluded from the analysis of the respective outcome and results will be reported for cases with available outcome information.

Interim Analyses
There will be no interim analysis.

Statistical Analytical Issues
Multiple Comparisons: There will be no adjustment for multiple testing. Results of secondary outcomes and post hoc analyses will therefore be considered exploratory.

Post-hoc analyses
Post-hoc data-driven analyses are allowed after the following are undertaken:

1. Document which analyses were conducted after the results for the primary and secondary outcomes are analysed.
2. Document the rationale for these analyses.
3. Pre-specify their interpretation in the context of the primary and secondary results and their impact on the overall trial conclusions.

References

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