PROTOCOL

Background

1. Provide the scientific background, rationale and relevance of this project.

The management of septic shock has evolved since the inception of the Surviving Sepsis Campaign with short-term mortality rates improving markedly in recent years [1]. Still, the costs of survived septic shock, both financial and otherwise, are legion and include utilization of limited ICU resources, concern over growing antimicrobial resistance, ICU-delirium together with its sequelae and the morbidity associated with standard medical and ancillary care such as central-line associated blood stream infections (CLABSIs).

Specifically, rates of central venous catheter (CVC) related infections are associated with increased duration of catheterization as reported in the literature and as reflected in the metric employed to track CLABSI rates, namely *rate per 1000 central line days*[2]. Because a significant indication for CVC placement and maintenance in patients with septic shock is the requirement for intravenous (IV) vasopressors, strategies designed to shorten the duration of IV vasopressor therapy may directly impact the length of time that CVCs remain in place and, in turn, decrease CLABSI rates. Moreover, anticipated indirect effects of shortened CVC dwell times include decreased ICU length-of-stay (LOS), rate of ICU-delirium, and hospital LOS.

Midodrine is an orally available vasopressor currently FDA-approved for orthostatic hypotension. However, accumulating literature supports the use of midodrine for the purpose of decreasing intravenous vasopressor requirements in diverse ICU populations, including surgical, cardiac and medical.

Midodrine is an oral prodrug which is believed to undergo enzymatic activation to desglymidodrine, an alpha-1 receptor agonist. The prodrug has an oral bio-availability of 93% with time to peak concentration of 1 to 2 hours for the active metabolite and a half-life of 3-4 hours. Both prodrug and active metabolite are renally excreted and dialyzable. Although, as stated previously, midodrine carries FDA-approval for orthostatic hypotension, it has been used off-label for dialysis-associated hypotension and for hypotension in the ICU-setting where its use has increased 7-fold in in recent years according to one study[3].

A growing body of literature comprising largely retrospective data seems to support the safety and efficacy of midodrine in the intensive care unit for decreasing IV vasopressor use[3-5]. In the largest retrospective case series to date, Rizvi et al. report that in 663 patients receiving IV vasopressors (in both surgical and medical ICU settings), 48% were liberated from IV vasopressor support within 24 hours of midodrine initiation. Regarding its efficacy in septic shock, Whitson et al. compared a retrospective cohort of patients in the "recovery phase" of septic shock receiving IV vasopressors and midodrine with a comparator cohort of patients receiving only IV vasopressors for the same indication. When compared with the IV vasopressor-only group, a statistically significant decrease in IV vasopressor duration approaching 24 hours was observed in the group receiving midodrine. Additionally, a decrease in ICU-LOS of nearly 2 days was

reported in the group receiving IV vasopressors and midodrine when compared with IV vasopressor-only group[5]. Finally, in a small but prospectively-designed study of 20 patients in a surgical ICU setting receiving a IV vasopressors at a mean phenylephrine equivalent rate of 41 mcg/min, the authors reported a significant acceleration in the decline rate of IV vasopressors[6].

Importantly, complications attributable to midodrine in the above studies were minor and predominantly consisted of asymptomatic bradycardia, an expected effect of the drug. It is noteworthy that an emerging body of evidence suggests that heart rate control and relative bradycardia are associated with improved outcomes in patients with septic shock[7,8]. Other adverse events reported have included ischemic bowel in 2 patients (0.18% of the study population), however, these events were not believed to be directly attributable to midodrine, and midodrine was only discontinued in one of these 2 patients[3].

On the basis of the described, pre-existing evidence, we hypothesize that administration of midodrine in the early phase of septic shock in patients with adequate enteral access will result in a significant decrease in time to IV vasopressor liberation (increase in vasopressor-free days), secondarily resulting in decreased CVC dwell times and ICU LOS. We aim to perform a randomized, double-blind, placebo-controlled trial to investigate the efficacy of midodrine in decreasing time to IV vasopressor liberation in patients with septic shock.

Study Design: Biomedical

1. Will controls be used?

Yes

►IF YES, explain the kind of controls to be used.

The control group will receive placebo on the same schedule that the investigational agent is administered, namely every 8 hours for 72 hours. The placebo will be prepared by our investigational pharmacy and dispensed by the same.

2. What is the study design?

Randomized, Double-Blind Placebo-Controlled Trial

3. Does the study involve a placebo?

Yes

►IF YES, provide a justification for the use of a placebo

Placebo is justified to provide for blinding of the nursing staff and study investigators who might otherwise confound study results by weaning vasopressors more or less aggressively than usual practice.

Human Participants

Ages: __18-89 years of age__
Sex: __BOTH__
Race: ___ANY_

Subjects- see below

1. **Provide target # of subjects (at all sites) needed to complete protocol.**

   To estimate the sample size, we used the UVA Clinical data repository (CDR) to identify 960 patients who would have met our study enrollment criteria (patients receiving IV vasopressors for >3 hours, with a diagnosis of sepsis, without cirrhosis, and not receiving midodrine). We then extracted their duration of vasopressors and the total norepinephrine equivalent doses at 24 hours. We performed repeated simulation of bootstrapped samples to estimate power from these populations with varying sample and effect sizes. Based on these estimates, we believe that a final sample size of 50 per group will provide 80% power to detect a 12-hour difference in duration of IV vasopressors based on a 2-arm study design (placebo vs midodrine). These calculations compare favorably with those obtained assuming a normal distribution, based on a mean IV vasopressor duration of 54.9 hours (SD 28.4 h) in patients with septic shock as published in a recent trial[9], which calculations would require randomization of 49 patients to each group to detect an effect of 18 hours difference in IV vasopressor duration at a power of 80% and an alpha value of 0.05. However, because our calculations are based on internal data (and so should reflect out practices of vasopressor weaning) and because the distribution of IV vasopressor duration is non-normal, we believe that sample size calculation based upon our CDR analysis is more accurate.

   To address questions regarding dosing both in terms of efficacy and safety, we will plan for an "early phase" of the study, which will essentially serve as a nested dose-response study. In this "early phase" we will randomize the first 45 subjects to one of 3 study arms (placebo, midodrine 10 mg thrice daily or midodrine 20 mg thrice daily). For the interim analysis of this "early phase", a final sample size of 15 patients per group will provide 80% power to detect a 5 mcg/min decrease in norepinephrine equivalents at 24 hours.

   Together with our "early phase" nested study and anticipating a 25% mortality in patients with septic shock we would need to enroll 115 patients to reach statistical significance. Enrolling 115 patients would allow randomization of 50 patients to placebo and 50 patients to the midodrine dose continued following the "early phase" (either 10 or 20 mg depending on the results of our interim analysis at which time we will evaluate both the safety and efficacy of both dosing strategies and continue the lowest dose that is both safe and efficacious). The additional 15 subjects would be required for the early dose-response portion of the study.

   In brief:

   115 total subjects: 50 placebo, 50 midodrine (either 10mg or 20mg); 15 additional subjects for the "early phase" portion of the study

2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**

   Average mortality in septic shock is anticipated to be around 25-30%. Screen failure is anticipated to be around 20%, mostly due to patients with decompensated cirrhosis. This is based on our MICU septic shock database.

3. **How many subjects will be enrolled at all sites?**
   149
4. **How many subjects will sign a consent form under this UVa protocol?**
   149

Inclusion/Exclusion Criteria

1. **List the criteria for inclusion**
   - Patients aged ≥18-89 years old
   - Admitted to UVA medical ICU with diagnosis of septic shock.
   - Patients requiring at least 5 mcg/min norepinephrine infusion (or equivalent) for blood pressure support for at least 3 hours
   - Patients with enteral access established within 12 hours of admission (either able to swallow, or feeding tube in place)

2. **List the criteria for exclusion**
   - Pregnant females; (due to the potential adverse effects to an unborn child); patients with childbearing potential will have results of pregnancy test checked (which is routinely performed on admission); should the patient have child-bearing potential and the pregnancy status is not checked as part of routine care, such patients will be excluded from the study (i.e. pregnancy testing will not be performed for research purposes)
   - Patients < 18 years
   - Prisoners
   - Patients already taking midodrine
   - Patients with cirrhosis of the liver as defined by either biopsy, imaging findings of cirrhosis AND thrombocytopenia or patients otherwise undergoing liver transplant evaluation
   - Patients with Increased intraocular pressure and glaucoma
   - Patients with allergy to midodrine
   - Non-English speaking patients, due to the narrow time-frame for study enrollment and execution of study protocol, employing interpreters is deemed to be a significant burden on the investigators with potential to hamper study enrollment. Non-english speaking patients are not deemed to be adversely affected by exclusion from study as there is no clear *a priori* reason why study results would not also apply to non-English speakers.
   - Patients without enteral access within 12 hours of initiation of IV vasopressors
   - Patients where the attending physician does not clinically intend to target a mean arterial pressure of > 65 mmHg
   - Patients with pheochromocytoma or thyrotoxicosis
   - Patients with active bowel ischemia

3. **List any restrictions on use of other drugs or treatments**.

Dihydroergotamines, digoxin and other cardiac glycosides. The use of drugs that stimulate alpha-adrenergic receptors (e.g., phenylephrine, pseudoephedrine, ephedrine, phenylpropanolamine or dihydroergotamine) may enhance or potentiate the pressor effects of Midodrine HCl.

Therefore, caution will be used when Midodrine HCl tablets are administered concomitantly with agents that cause vasoconstriction. However, the aim of midodrine in this trial is to potentiate vasoconstriction to treat the hypotension associated with septic shock and it will be cautiously used with phenylephrine, norepinephrine, epinephrine, vasopressin, ephedrine, or pseudoephedrine.

Although the following considerations are important when used for orthostatic hypotension these are not clinical concerns when using the agent in septic shock.

- Midodrine HCl has been used in patients concomitantly treated with salt-retaining steroid therapy (i.e., fludrocortisone acetate), with or without salt supplementation. The potential for supine hypertension exists in these patients and may be minimized by either reducing the dose of fludrocortisone acetate or decreasing the salt intake prior to initiation of treatment with Midodrine HCl.
- Alpha-adrenergic blocking agents, such as prazosin, terazosin, and doxazosin, can antagonize the effects of Midodrine HCl.

Patients will be continuously monitored in ICU and the goal of the study is to raise blood pressure.

Statistical Considerations

1. Is stratification/randomization involved?

YES

►IF YES, describe the stratification/ randomization scheme.

After enrollment, patients will initially be randomized employing a block of 9 randomization scheme generated by the study investigators. Allocation will be performed manually; there will be 5 envelopes, each envelop for a sequence of 9 patients. Each envelope will contain 3 cards for the placebo group and 3 cards for the midodrine 10 mg TID treatment group and 3 cards for the midodrine 20 mg TID treatment group. Cards will be pulled out of the envelope to randomize the patients. Once 9 patients are randomized the next envelop will be opened.

Following interim analysis of the first 45 patients, one of the treatment groups will dropped with preference given to dropping the midodrine 20 mg TID group should interim analysis demonstrate similar, significant effect sizes in both treatment groups. Additionally, the safety profile of both dosing strategies will be considered prior to continuing the experimental arm of the study.

Subsequently, the remaining 104 patients will be randomized employing a block of 8 randomization scheme generated by the study investigators. Allocation will be performed manually; there will be 13 envelopes, each envelop for a sequence of 8 patients. Each envelope will contain 4 cards for the placebo group and 4 cards for the continuing midodrine group (either 10 mg TID or 20 mg TID). Cards will be pulled out of the envelope

to randomize the patients. Once 8 patients are randomized the next envelop will be opened.

►**IF YES, who will generate the randomization scheme?**

_____ Sponsor
_____ UVa Statistician. Insert name Answer/Response:
__X___ _____ UVa Investigational Drug Service (IDS)
___ x__ Other*:* Specify Answer/Response: Investigators UVa Investigational Drug Service (IDS)

2. What are the statistical considerations for the protocol?

We will compare placebo group versus the midodrine intervention group for all primary analyses and use the Mann-Whitney U test to assess the primary outcome, which is assumed to be non-parametric.

3. Provide a justification for the sample size used in this protocol.

To estimate the sample size, we used the UVA Clinical data repository (CDR) to identify 960 patients who would have met our study enrollment criteria (patients receiving IV vasopressors for >3 hours, with a diagnosis of sepsis, without cirrhosis, and not receiving midodrine). We then extracted their duration of vasopressors and the total norepinephrine equivalent doses at 24 hours. We performed repeated simulation of bootstrapped samples to estimate power from these populations with varying sample and effect sizes. Based on these estimates, we believe that a final sample size of 50 per group will provide 80% power to detect a 12-hour difference in duration of IV vasopressors (our primary end point) based on a 2-arm study design (placebo vs midodrine). These calculations compare favorably with those obtained assuming a normal distribution, based on a mean IV vasopressor duration of 54.9 hours (SD 28.4 h) in patients with septic shock as published in a recent trial[9], which calculations would require randomization of 49 patients to each group to detect an effect of 18 hours difference in IV vasopressor duration at a power of 80% and an alpha value of 0.05. However, because our calculations are based on internal data (and so should reflect out practices of vasopressor weaning) and because the distribution of IV vasopressor duration is non-normal, we believe that sample size calculation based upon our CDR analysis is more accurate.

To address questions regarding dosing both in terms of efficacy and safety, we will plan for an "early phase" of the study, which will essentially serve as a nested dose-response study. In this "early phase" we will randomize the first 45 subjects to one of 3 study arms (placebo, midodrine 10 mg thrice daily or midodrine 20 mg thrice daily). For the interim analysis of this "early phase", a final sample size of 15 patients per group will provide 80% power to detect a 5 mcg/min decrease in norepinephrine equivalents at 24 hours.

Together with our "early phase" nested study and anticipating a 25% mortality in patients with septic shock would need to enroll 149 patients to reach statistical significance.

Secondary outcomes will include ICU and hospital length of stay as well as central venous catheter dwell time. Because IV vasopressor duration cannot be assumed to have a normal distribution, we intend to analyze our primary outcome using the Mann-Whitney U test.

4. What is your plan for primary variable analysis?

Dose of IV vasopressor(s) at 24 hours and hours requiring IV vasopressor therapy will be the primary outcomes of interest for the "early phase" and complete study, respectively. Because IV vasopressor duration and dose cannot be assumed to have normal distributions, we intend to analyze our primary outcome using the Mann-Whitney U test.

5. What is your plan for secondary variable analysis?

1. Central venous catheter free days
2. Hospital length of stay
3. Intravenous Vasopressor free days
4. 28-day mortality
5. ICU mortality
6. Need for re-initiation of vasopressor therapy after discontinuation for >2 hours

We will employ the Chi square test for binary outcomes. Furthermore, we will use regression analyses with appropriate interaction terms.

6. Have you been working with a statistician in designing this protocol?

No

IF YES, what is their name?

Answer/Response:

N/A

7. Will data from multiple sites be combined during analysis?

No

INSTRUCTIONS: IF YES, answer the following questions

7(a). Does the study involve randomization?

Answer/Response:

IF YES, will randomization be done at each site or among sites?

Answer/Response:

7(b). Has the sample size calculation considered the variation among sites?

Answer/Response:

7(c). When combining the data from multiple sites to assess the study results, is the effect of the treatment to be tested (or the association to be tested) assumed to be the same across sites or vary among sites? What is the modelling strategy?

Answer/Response:

7(d). Is there a common protocol used in all sites?

Answer/Response:

IF NO, how will differences among sites, such as those related to the implementation, inclusion criteria, patient characteristics, or other sites characteristics, be considered to assess the study results?

Answer/Response:

Study Procedures-Biomedical Research

1. What will be done in this protocol?

Screening:

Patients admitted to the ICU with a diagnosis of sepsis and in shock as defined, for study purposes, as requiring any IV vasopressor of at least 5 mcg/min norepinephrine infusion (or equivalent) for at least 3 hours AND with adequate enteral access (oral, orogastric, nasogastric or pre-existing PEG, will be screened by research nurse, study coordinator or study investigator by review of medical record in EPIC only. If subject meets study criteria then the research nurse, study coordinator or investigators will approach patient or surrogate for consent to participate in the study. For patients unable to provide consent due to illness, surrogate consent will be sought.

Following consent, women of childbearing potential will have a urine pregnancy test. Pregnant women will be excluded.

Study Treatment:

In the "early phase" the first 45 subjects will be randomized to one of 3 study arms (placebo, midodrine 10 mg or midodrine 20 mg thrice daily for 72 hours). The remaining 104 subjects will subsequently be randomized to one of 2 study arms, placebo or the more efficacious of the 2 midodrine doses (10 mg TID or 20 mg TID) as determined by the planned interim analysis.

Data collection from the subject's medical record will continue until hospital discharge. Data to be collected will include the following:

1. Vasopressor(s) used by type
2. Vasopressors dose and duration
3. ICU and hospital length of stay
4. Basic lab values including CBC, makers of renal function, cardiac biomarkers (troponin, BNP)
5. Presence of central venous catheter, site and number
6. CVC dwell time
7. GCS
8. APACHE IV scores
9. Blood gas data
10. Mortality data (30- and 90-day)
11. Culture data

12. Diagnosis data pulled from provider notes
13. MAR data including concomitant corticosteroid use and antibiotics
14. Imaging data, including CXRs and CTs
15. Vital sign data including temperature, heart rates, blood pressures for the duration of the admission

The standard current ICU level care will be provided to both study groups. Invasive blood pressure measurement, laboratory studies, and imaging studies will be done according to standard practices in septic shock for all groups in the trial.
Intravenous vasopressor will be weaned in both groups as tolerated for MAP goal of > 65 mmHg by the bedside nursing staff according to usual practice (no protocolized algorithm for vasopressor weaning exists, vasopressors are weaned, as long as targeted MAPs are maintained, according to nursing judgment.

Subjects admitted to the ICU with a diagnosis of sepsis and in shock as defined, for study purposes, as requiring any IV vasopressor of at least 5 mcg/min norepinephrine infusion (or equivalent) for at least 3 hours AND with adequate enteral access (oral, orogastric, nasogastric or pre-existing PEG) will be randomized to either midodrine 10 or 20 mg every 8 hours for 72 hours or placebo, to investigate the efficacy of midodrine in decreasing time to IV vasopressor liberation in patients with septic shock. Data collection will continue until hospital discharge.

A dose of up to 20 mg TID is chosen as it was the modal dose in a recent prospective study and is the upper end of dosing with predictable hemodynamic response in another study. The retrospective studies previously referenced reported varying doses up to 40 mg TID.

The standard current ICU level care will be provided to both study groups. Invasive blood pressure measurement, laboratory studies, and imaging studies will be done according to standard practices in septic shock for both arms of trial. Intravenous vasopressor will be weaned in both groups as tolerated for MAP goal of > 65 mmHg by the bedside nursing staff.

2. **If this protocol involves study treatment, explain how a subject will be transitioned from study treatment when they have completed their participation in the study.**

   Subjects will receive the study drug or placebo for a pre-specified duration of 72 hours. We acknowledge that discontinuation of the study drug may result in the need to resume IV vasopressor therapy, however reinitiation of IV vasopressor therapy will be one of the secondary outcomes under study. Re-initiation of IV vasopressor therapy cannot strictly be considered a risk of study treatment as the rate of re-initiation of IV vasopressors in the reference group is not technically known and care providers (not study investigators) may opt to start midodrine in an unblinded manner rather than re-initiating IV vasopressor therapy.

Subject Compliance with Study Procedures

1. **Explain how the study team will monitor the subject for compliance with the study procedures.**

(e.g. study team will administer study drug/ study interventions, study drug inventory of dispensed and returned drug, diary etc.)
The study team, nursing staff and/or the investigational pharmacy (IDS) will keep a log.

2. **Describe criteria for when a subject is considered to be non-compliant with study procedures.**
(e.g. subject returns more than 20% of the study drug, subject misses 20% of study visits)
Non-compliance will considered inability to administer more than 20% of the scheduled drug or placebo.

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