**A Pilot, Randomised Controlled Trial of Midodrine as an Adjunctive Vasopressor for Fluid-Refractory Hypotension in Intensive Care Patients**

*Short title:* ***M****idodrine as an* ***A****djunctive* ***V****asopr****E****ssor for* ***R****efractory Hypotension in* ***I****ntensive* ***C****are (MAVERIC) Study*

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**LAY SUMMARY**

Low blood pressure (hypotension) that does not improve with administration of fluids is a common reason for admission to intensive care. These patients usually require drugs that tighten blood vessels (vasopressor) to be given by continuous drip into a vein (intravenous infusion) to support the circulation and maintain a sage blood pressure for a period of time until the patient improves. Underlying causes of this hypotension may relate to sepsis, inflammatory conditions such as pancreatitis, use of medications and inflammation as sometimes seen in patients after surgery.

Midodrine is a drug that tightens blood vessels that can be taken by mouth and has been successfully used in many patients with diseases that cause low blood pressure and faintness when standing (orthostatic hypotension). It can be given as a tablet and is well tolerated. Recent studies have focused on its use in patients with other causes of hypotension and suggest it may be safely used in critically unwell patients already receiving vasopressor infusions for hypotension to shorten the length of time requiring such infusions. This may have additional patient benefits with shorter length of time of invasive monitoring and shorter length of ICU and hospital stay. There are, however, no randomised controlled trials assessing this effect, making it unclear whether reports published so far are correct.

We aim to compare the effect of midodrine added to usual care against usual care in critically ill patients on low dose vasopressor infusions for fluid-unresponsive hypotension. We plan to enrol a total of thirty patients who have required a vasopressor infusion for more than 24 hours and remain on an infusion due to continuing hypotension. These thirty patients will be randomly (like the toss of coin) assigned to receive either midodrine in three divided doses of 10 mg each per day or usual care. To understand the effect of the midodrine administration, we will record routinely recorded patient demographic data, circulation data (such as blood pressure, heart rate, central venous pressure and cardiac output), baseline laboratory data (haemoglobin, white cell count, alanine aminotransferase, international normalised ratio, bilirubin, urea, creatinine, troponin, lactate), urine output and fluid balance and dose of intravenous vasopressor. The primary outcome measure will be time in hours from initial administration of Midodrine to cessation of intravenous vasopressor. Secondary outcome measures, such as length of ICU and hospital stay, will also be recorded. The results of this study will provide insight into the effects of midodrine in attenuating duration of vasopressor infusions in intensive care patients with fluid resistant hypotension and, if positive, will allow our patients to be able to stop their infusion and return to the ward and home more quickly.

**1. INTRODUCTION**

Refractory hypotension is defined as a systolic blood pressure of less than 90 mmHg or a mean arterial pressure of less than 65 mmHg after an intravenous fluid challenge of 1000 mL or more administered within a 60-minute period1. If the underlying cause is due to a distributive shock state, patients often require intravenous vasopressors to support their blood pressure and this remains one of the most common indications for admission to an intensive care unit2. As these patients stabilise following resuscitation and targeted medical therapy, their vasopressor requirements reduce, but they may continue to require a low-dose intravenous vasopressor for a period of time (often days). Hospital policy dictates that these patients must remain in a critical care environment for close observation and monitoring during this period. One possible solution to this problem is the replacement of the intravenous vasopressor with an oral agent to facilitate an earlier discharge from the critical care environment.

Midodrine is a potent, peripherally-acting α-receptor agonist. After oral administration it causes modest increases in supine and standing blood pressures in a dose-dependent manner3. Its common adverse effects are related to its α-agonist properties and include piloerection, pruritus, paraesthesia and urinary retention4. Such side effects, however, are uncommon (< 5%). The most common adverse event is supine hypertension, but in patients who are profoundly hypotensive in ICU and who have continuous blood pressure monitoring, this is unlikely to be a problem.5 Another known but uncommon side effect is bradycardia. However, all ICU patients’ heart rate is continuously monitored ensuring that appropriate cessation can be rapidly implemented. It appears to have no central nervous system activity and does not affect pulmonary or renal function, bone marrow, blood coagulation or fibrinolysis. It is rapidly and almost completely absorbed in healthy volunteers, achieving a maximum plasma concentration of about 10 to 50 µg/L within 40 minutes. Midodrine undergoes enzymatic hydrolysis in the systemic circulation to release its pharmacologically active metabolite, de-glymidodrine, of which peak plasma concentrations are reached about 1 hour after a single dose. Absolute bioavailability of midodrine is 93% for oral tablets and 90% for oral solution. Midodrine is cleared from plasma after 2 hours (elimination half-life of 30 minutes). It undergoes extensive metabolism, with only 2 to 4% of a single dose excreted unchanged. Midodrine and de-glymidodrine are primarily renally excreted3.

Midodrine has previously been evaluated in a variety of clinical settings, including the management of orthostatic hypotension6,7, neurocardiogenic syncope8, dialysis-induced hypotension9, as a substitute for albumin in abdominal paracentesis-related hypotension10 and in post-operative settings for carotid artery stenting11 and spinal surgery12. There is also an ongoing before-and-after study at the Austin Hospital with post-operative orthopaedic patients receiving midodrine for SIRS-related hypotension (LNR/17/Austin/12), in which midodrine has proved safe. Importantly, no significant adverse effects have been reported in any of these studies. In critical care settings, midodrine has been safely utilised to wean patients off noradrenaline, phenylephrine, vasopressin and dopamine in small case series13, small prospective observational studies14,15 and larger retrospective case-control16 and cohort studies17. Such studies have involved hundreds of patients without any safety concern. The addition of oral midodrine, therefore, may be a solution to reduce the duration of time patients with refractory hypotension remain on intravenous vasopressors and their ICU and hospital length of stay. There are, however, no published randomised controlled trials assessing and quantifying this effect to date.

**2. STUDY AIM AND OBJECTIVES**

The aim of this study is to assess whether the use of adjunctive midodrine in patients with vasopressor-dependent hypotension reduces the time to cessation of intravenous vasopressor.

The primary outcome measure will be time to cessation of intravenous vasopressor use. Secondary outcome measures will be length of ICU stay, length of hospital stay, rate of ICU readmission and rate of adverse effects deemed by the treating clinician to be potentially related to the use of midodrine.

**3. METHODOLOGY**

**Study design**

This is a pilot randomised controlled trial.

Patients with refractory hypotension on an intravenous vasopressor for more than 24 hours but deemed clinically stable by the treating clinician and receiving no more than 10 mcg/min of noradrenaline infusion or no more than 100 mcg/min of metaraminol infusion will be eligible to be enrolled in this study.

After screening to confirm eligibility the patient will be randomly assigned to receive either midodrine 10 mg t.d.s. to be administered concurrently with ongoing intravenous vasopressor therapy or to receive usual care. All other treatment and investigations will remain equal. The administration of this medication will occur in a random fashion.

The study drug will be weaned once the primary outcome is reached (cessation of intravenous vasopressor) at the following rate:

* 10 mg t.d.s. for the first 24 hours after cessation of intravenous vasopressor
* 7.5 mg t.d.s for the following 24 hours
* 5 mg t.d.s for the following 24 hours (48 hours after cessation of intravenous vasopressor)
* Cessation of midodrine (72 hours after cessation of intravenous vasopressor)

The study drug will be ceased immediately if an adverse event occurs (i.e. new or worsening organ failure, allergic reaction, high blood pressure).

**Setting and sample size**

A sample of forty (40) patients admitted to the Department of Intensive Care, Austin Hospital will be enrolled into this study. The following eligibility criteria will be applied in order to identify the sample:

*Inclusion Criteria*

* Admission to the Austin Hospital ICU
* Age 18 years or greater
* Refractory hypotension (as defined above), requiring treatment with a single intravenous vasopressor at low dose (as defined above)

*Exclusion Criteria*

* Known allergy to midodrine
* Clinical haemodynamic instability, including high vasopressor requirement (i.e. noradrenaline > 10 mcg/min; metaraminol > 100 mcg/min)
* Severe shock state, as evidenced by a lactate > 4 mmol/L or multiple vasopressor infusions
* Renal failure as evidenced by a creatinine > 150 µmol/L
* Alternate treatable cause for refractory hypotension (i.e. bleeding, hypovolemic shock, cardiogenic shock, obstructive shock)
* Patients with liver failure, severe heart disease, pregnancy, thyrotoxicosis
* Acute brain pathology in which the treating clinician deems in inadvisable to enrol the patient, for example subarachnoid haemorrhage or those with current cerebral perfusion pressure (CPP) therapies in place
* Bradycardia, heart rate less than 50 bpm
* Those being feed via a jejunal tube
* Those with no enteral route available

**Enrolment and Randomisation (including envelope preparation)**

The study investigators will be responsible for enrolling patients. Patients will be randomly assigned in a 1:1 ratio to receive either midodrine or usual care. Randomisation will be performed with the use of a computer-generated randomization list with permuted blocks of 2 or 4 or 6 patients also in random sequence. Allocation will be concealed in sequentially numbered sealed, opaque envelopes to be opened after consent it obtained. An un-blinded member of the research team will be responsible for the preparation of the randomisation envelopes which is consistent with previous site procedures. Once prepared a research team member not caring for the participant will be responsible for the sequential selection and use of each envelope for the purposes of randomisation and treatment allocation identification.

**Data Collection**

For all patients, the following variables will be collected:

Demographics

* Gender
* Date of birth
* Body weight
* Height
* Pre-existing documentation of hypertension
* Document current use of corticosteroids

Baseline co-morbidities and physiological status

* Chronic APACHE co-morbidities
* Vital signs – heart rate, blood pressure, oxygen saturation (SpO2), respiratory rate, temperature, urine output
* Baseline arterial blood gas pH
* Baseline lactate
* Baseline urea and creatinine
* Baseline electrolytes
* Baseline liver function tests
* Baseline random cortisol level

Haemodynamic and physiological parameters while in the intensive care unit

* Heart rate and blood pressure during the period of the study
* The amount of vasopressor used during the period of the study
* The amount of intravenous fluid given during the period of the study
* The amount of sedation used during the period of the study
* Level of supplemental oxygen or ventilatory support

Biochemical data while in the intensive care unit

* Arterial blood gases
* Lactate
* Urea and creatinine
* Electrolytes
* Liver function tests

Hospital utilisation

* Duration of ICU stay
* ICU discharge status (alive or dead)
* Duration of hospital stay
* Hospital discharge status (alive or dead)

Additionally, patients will be monitored for development of new organ failure as defined by:

* Acute kidney injury – doubling of serum creatinine or oliguria with urine output < 0.5 mL/kg/hr for > 12 hours
* Deranged liver function – levels of either AST or ALT exceeding twice the upper limit of normal
* Worsening respiratory failure – worsening P/F ratio

**4. DATA ANALYSIS**

**Power calculations**

The sample size estimation is informed by the previous observational study by Whitson et al17. In this study, the duration of vasopressor therapy was 2.9 days compared with 3.8 days with no midodrine. Assuming a similar difference in our study and standard deviation of one day in each group. A study of 30 patients will have an 80% power to detect such a 0.9 days difference at an alpha of 0.05. We plan to randomize 34 patients to compensate for possible consent withdrawal or protocol deviations.

**Baseline Characteristics**

Variables will be assessed for normality and log-transformed if appropriate. Baseline comparisons will be performed using Fisher’s exact tests and reported as n (%). Continuous normally distributed variables will be compared using Student t-tests and reported as means (standard deviation), while non-normally distributed data will be compared using Wilcoxon rank-sum tests and reported as medians [interquartile range].

**Study analysis**

The study analysis will be by intention to treat. We will analyse our data using the log-rank test to determine whether time from initiation of midodrine until discontinuation of IV vasopressors and ICU and hospital length of stay differs between groups. Using Fisher’s exact test, we will test whether rates of ICU readmission and incidence of adverse events is different between treatment groups. All comparisons of continuous variables related to secondary outcomes will be by non-parametric statistics. All comparisons of ordinal variables related to secondary outcomes will be by Fisher’s exact test. A p value of < 0.05 will be considered statistically significant. All analyses will be conducted by a statistician blinded to intervention group assignment.

**5. PATIENT CARE**

With the exception of randomisation to either receive midodrine or usual care, patient care shall not be affected in any other way. We will not control or modify any other part of the treatment or care plans of the patient.

**6. ETHICS APPROVAL AND CONSIDERATION**

The major ethical issues in this study relate to the fact that participants involved in the study will be patients who are critically unwell and unlikely to be able to give informed consent. Consent is a foremost consideration in the conduct of this clinical trial. The expectation of consent is to obtained informed consent from the participant or their person responsible/medical treatment decision maker in a timely fashion.

The process for obtaining consent will be according to the following hierarchy.

1. *Consent*: Where possible and practicable for the patient to consider the study and give consent within an appropriate timeframe, the patient will be approached as asked to provide informed consent in accordance with the requirements of the Austin Health Human Research Ethics Committee and applicable legislation.
2. *Informed consent from the person responsible/Medical Treatment Decision Maker:* Where possible, and as authorized by Victorian law, consent will be obtained from the participant’s legally authorized representative.
3. *Delayed consent*: Where it is not possible or practicable for the patient or person responsible/medical treatment decision maker to consider the study and give consent within an appropriate timeframe, the patient may be enrolled without prior consent, provided the procedure is in accord with the requirements of the Austin Health Human Research Ethics Committee and applicable legislation. Where appropriate, the person responsible, and in turn, the participant, will be informed of the study and will be able to withdraw consent for ongoing participation at any time. The timeframe expect for the conversation with the person responsible/medical treatment decision maker is within the first 72 hours of enrolment.
4. Once participants are recovered and are able to consider the information sheet, they will be offered the opportunity to withdraw from the study follow-up. This may occur during the participant’s admission to the intensive care unit or shortly after during the participant’s stay in the hospital ward setting.
5. If the patient dies due to the nature of their critical illness before consent was able to be obtained from the person responsible/medical treatment decision maker then consent for the use of data will be sought from the Austin Health Human Research Ethics Committee via a waiver of consent request. Each request will be made on an individual participant basis in accordance with Austin Health’s process for applying for a waiver of consent.

**7. CONFIDENTIALITY OF PATIENT DATA**

Participants will not be identified by name, and confidentiality of information in medical records will be preserved. All patients’ details will be entered in coded format. The confidentiality of the participant will be maintained unless law or other regulations require disclosure.

**8. SAFETY ISSUES**

Midodrine is currently used and well tolerated in patients with orthostatic hypertension6,7. This medication and dosage has been trialled in a cohort of patients at the Austin Hospital in an ongoing study without significant adverse events (LNR/17/Austin/12). Furthermore, this medication has also been trialled in large patient cohorts receiving concurrent intravenous vasopressor infusions with minimal reported adverse effects14,15,16,17. As such, we do not anticipate any significant safety issues with this trial.

The patient will be kept in the ICU for a period of observation of at least 8 hours following cessation of intravenous vasopressor to reduce the likelihood of hypotension or other side effects on discharge. Upon discharge from ICU, the accepting team will be informed that the patient has received a study drug and instructions will be given to medical and nursing staff to contact a study investigator if the subject becomes hypotensive in the 24 hours after ICU discharge (defined as a SBP < 90 mmHg).

Adverse events are defined as any unfavourable and unintended signs, symptoms or diseases chronologically associated with midodrine or placebo administration. Adverse events will be recorded daily. Nursing charts and documentation, as well as medical notes will be reviewed to identify potential adverse events. The relationship of any adverse event to the study drug will be assessed by a study investigator and qualified by strength of association and severity.

Serious adverse events are hypertension (systolic BP > 180 mmHg), bradycardia (heart rate < 40 beats per minute) or new organ failure (evidence of inadequate organ oxygenation, liver and renal failure as per definitions in exclusion criteria). It is recognised that the intensive care patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless the event requires significant intervention or are considered to be of concern in the investigator’s clinical judgement.

This is an investigator-initiated study being conducted at the Austin Hospital. There is no independent Data and Safety Monitoring Committee (DSMC) associated with the conduct of this study.

**9. INDEMNITY**

This is an investigator-initiated study and, accordingly, no commercial sponsor’s indemnity has been provided.

**10. DATA RETENTION, STORAGE, DESTRUCTION AND PUBLICATION**

Investigators will design the data collection forms. Patient clinical details and demographics will be recorded on these as well. Completed forms will be kept in the department of ICU at the Austin hospital. The collected data will then be stored on an electronic database on password-protected computers located within the ICU Research Office of Austin Health. Paper data and study related documents used in this study will be re-identified and only a master log will be maintained to identify participants and their study data. The log will be locked in a protected office. All data for this audit will be retained for a period of 15 years after which all electronic and paper data will be destroyed in accordance with hospital policy in place at the time. If the combination of these routinely collected data and information derived from this study provides useful clinical insights into the management of critically ill patients we plan to publish our findings.

**Patient safety and adverse event report**

Adverse or serious adverse events will be reported and recorded for reviews.

**Funding and Insurance**

This is an investigator-induced study and the funding is provided by Austin Hospital. As this study is performed in the public hospital, indemnity insurance shall be provided by the hospital.

**11. RESEARCH TIME-LINE**

*Proposed research time-line*

* March 2018: Submit protocol for HREC approval.
* June – August 2018: data collection and analysis.
* September – October 2018: data interpretation and manuscript preparation.
* November 2018: submit manuscript for publication in peer-reviewed critical care journal.

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