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Oral Midodrine Administration During the First 24 Hours of Sepsis to Reduce the Need of Vasoactive Agents: Placebo-Controlled Feasibility Clinical Trial

Amos Lal, MBBS, FACP[1]

Vrinda Trivedi, MBBS[2]

Mahrukh S. Rizvi, MD[3]

Amy Amsbaugh, RRT, LRT[4]

Melissa K Myers, MD[5]

Khaled Saleh, MD[6]

Rahul Kashyap, MBBS, MBA[7]

Ognjen Gajic, MD, MSc, FCCP, FCCM[8]

OBJECTIVES: Our preliminary data and observational studies suggested an increasing "off label" use of oral midodrine as a vasopressor sparing agent in various groups of critically ill patients, including those with sepsis. We designed this clinical trial to evaluate the feasibility of use of midodrine hydrochloride in early sepsis to reduce the duration for IV vasopressors and decrease ICU and hospital length of stay.

DESIGN: Pilot, two-center, placebo-controlled, double blinded randomized clinical trial.

SETTING: Medical ICUs at Mayo Clinic Rochester and Cleveland Clinic Abu Dhabi were the study sites.

PATIENTS AND METHODS: Adult patients (≥ 18 yr old) were included within 24 hours of meeting the Sepsis-3 definition if the mean arterial pressure remained less than 70 mm Hg despite receiving timely antibiotics and initial IV fluid bolus of 30 cc/kg.

INTERVENTION: Three doses of 10 mg midodrine versus placebo were administered.

MEASUREMENTS AND MAIN RESULTS: Total 32 patients were randomized into midodrine ($n = 17$) and placebo groups ($n = 15$). There were no major differences in baseline variables between the groups except for higher baseline creatinine in the midodrine group (2.0 ± 0.9 mg/dL) versus placebo group (1.4 ± 0.6 mg /dL), $p = 0.03$. The median duration of IV vasopressor requirement was 14.5 ± 8.1 hours in midodrine group versus 18.8 ± 7.1 hours in the placebo group, p value equals to 0.19. Patients in the midodrine group needed 729 ± 963 norepinephrine equivalent compared with 983 ± 1,569 norepinephrine equivalent in the placebo group, p value equals to 0.59. ICU length of stay was 2.29 days (interquartile range, 1.65–3.9 d) in the midodrine group, compared with 2.45 days (interquartile range, 1.6–3.2 d) in the placebo group, p value equals to 0.36. No serious adverse events were observed in either group.

CONCLUSIONS: Phase II clinical trial powered for clinical outcomes (duration of vasopressor use, need for central venous catheter, and ICU and hospital length of stay) is justified.

KEY WORDS: critical care; intensive care unit; midodrine; sepsis; vasopressors

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BACKGROUND

Epidemiologic studies suggest that global incidence of sepsis and severe sepsis in the last decade has been 437 and 270 per 100, 000 person-years, respectively (1). Sepsis is the second leading cause of death in medical ICUs and carries a mortality rate between 25% and 30% (2). In the United States, resource utilization for sepsis is higher than any other clinical condition warranting hospital admission and continues to rise. In 2013, sepsis accounted for $24 billion in hospitalization expenses (3). Clinical manifestations of sepsis are highly variable, and the presentation may vary depending on the underlying health status of the patient, presence of organ dysfunction, source of infection, and causative organism. Acute organ dysfunction most commonly affects the respiratory and cardiovascular systems (4). Cardiovascular compromise in sepsis manifests as hypotension due to arterial vasodilation, secondary to increased nitric oxide production and activation of potassium channels in vascular smooth muscle cells (5, 6). Current management of hypotension in sepsis is to start with fluid resuscitation in order to improve organ perfusion, in addition to appropriate source control, antibiotics, ensuring lactate clearance and to ensure mean arterial pressure (MAP) greater than 65 mm Hg. The overarching management focuses on maintaining organ perfusion by targeting a MAP greater than 65 mm Hg, initially through the administration of fluids (7). Despite appropriate fluid resuscitation, hypotension can persist, necessitating initiation of IV vasopressors such as norepinephrine, epinephrine, and vasopressin. Administration of IV vasopressor agents requires monitoring in the intensive care setting and preferentially placement of invasive vascular devices (central venous catheters) (8). In addition to known complications of central venous catheter placement (arterial puncture, infections, pneumothorax), the placement of the catheter itself is time consuming, resource intensive, and often associated with patient discomfort (9). This is particularly important in patients with respiratory distress in whom Trendelenburg or head down position required for catheter placement (internal jugular or subclavian venous access) can precipitate respiratory failure. In addition, continuous infusion of IV pressor agents can contribute to longer ICU and hospital lengths of stay (LOS) and increased cost (10, 11). On the other hand, the clinicians' hesitance to place invasive central venous access early in the course of sepsis often delays vasopressor administration with additional fluid boluses contributing to fluid overload and its complications (12).

Early diagnosis and treatment are synonymous with improved outcomes for many life-threatening conditions (13). It is to be expected that poor outcomes in sepsis and linked common ICU syndromes are at least in part due to suboptimal early management (8). Indeed, a failure to recognize and treat deteriorating patients accounts for an estimated 11% of total number of deaths in hospitalized patients (14). Although the definition and management of sepsis has received a lot of attention, therapies to decrease incidence of organ dysfunction and progression of sepsis to septic shock have not been studied as extensively. Similarly, no alternatives to IV vasopressor infusion have been studied in clinical practice. Recently, our preliminary data and observational studies suggested an increasing "off label" use of oral midodrine as a vasopressor sparing agent in various groups of critically ill patients, including those with sepsis (15–17). Midodrine has been studied as an adjunct for the treatment of refractory hypotension and as an adjunct for the weaning of vasopressor agents in the ICU (18–20). Studies have been undertaken in the postoperative and surgical ICU population, where it has been shown to liberate patients from IV vasopressors sooner (19–22). Midodrine has also been studied in patients with hepatorenal syndrome and cirrhosis, hemodialysis-induced hypotension, spinal cord injury, and orthostatic hypotension (23–25). Despite the currently available literature, robust evidence (in the form of clinical trials) supporting the use of midodrine in the early phase of sepsis in ICU setting has been lacking. Study by Santer et al (27) evaluated the utility of midodrine in ICU for the treatment of hypotension. However, due to heterogeneity of the study population, inability to use the benefits of midodrine in the first 24 hours and lack of an established protocol to wean vasopressors resulted in the lack of benefit for this subset of patients.

Although the available literature favors the off label use of midodrine to be used as a feasible adjunct or potentially an alternative (in certain cases) to IV vasopressor use, no randomized trial has been conducted to evaluate the feasibility of using midodrine specifically in patients with sepsis. To test the feasibility and determine the effect size for future phase II clinical trials, we conducted a placebo-controlled randomized controlled pilot study in two tertiary care ICUs.

PATIENTS AND METHODS

We conducted a pilot, two-center, placebo-controlled, double blinded, randomized clinical trial. The study was approved by the Mayo Clinic Institutional Review Board (IRB) (Rochester, MN, IRB number 16-002444) and Cleveland Clinic IRB, Abu Dhabi. There were no significant changes made to the trial design after its initiation. The study was funded by Mayo Clinic Critical Care intramural research grant. The trial was registered at ClinicalTrials.gov: NCT03129542.

Study Population

The study population included patients with diagnosis of sepsis who were admitted to the medical ICU from August 2017 until March 2020. Subjects met inclusion criteria if they had a MAP of less than 70 after receiving antibiotics and an initial IV fluid resuscitation with 30 mL/kg as per the surviving sepsis guidelines, before the first dose of the study drug or placebo can be administered (**Fig. 1**). Patients were electronically screened for enrollment in the emergency department (ED) or the ICU when they met criteria for sepsis. Our study coordinators along with a coinvestigator physician member of the study team screened patients for eligibility by using the electronic databases in the ED or ICU (**Fig. 2**). We used the Sepsis-3 definition to assess for presence of sepsis. Once eligibility criteria were met, subjects were offered to participate in the trial, and consent was obtained (either from the patient or the legal power of attorney). Subjects were randomized in a double blind fashion to either the placebo or midodrine groups. Random allocation sequence was generated using a randomization generator software in conjunction with colleagues from biostatistics and was conveyed to the research pharmacy team. Three doses of either placebo or midodrine 10 mg were administered orally every 8 hours, in addition to usual care for sepsis. This dose was chosen keeping in mind the side effects to midodrine such as bradycardia and masking the signs of hypoperfusion as seen in other studies (17, 26). The medical provider, nursing staff, and patient were blinded to randomization; only research pharmacists were aware of randomization. Blood pressure was recorded every 4 hours for the first 24 hours from the time of administration of the first dose and just prior to administration of each dose. Subsequent doses were held if systolic blood pressure was found to be greater than 130 to avoid hypertensive episodes. Since this was only a feasibility trial, there was no further intervention after all three doses had been administered; however, clinical outcomes and adverse events (AEs) were monitored. Both the groups were monitored for occurrence of any potential AEs attributable to midodrine during the first 48 hours of study drug administration and then daily for the next 7 days. The list and definition of AEs is as below:

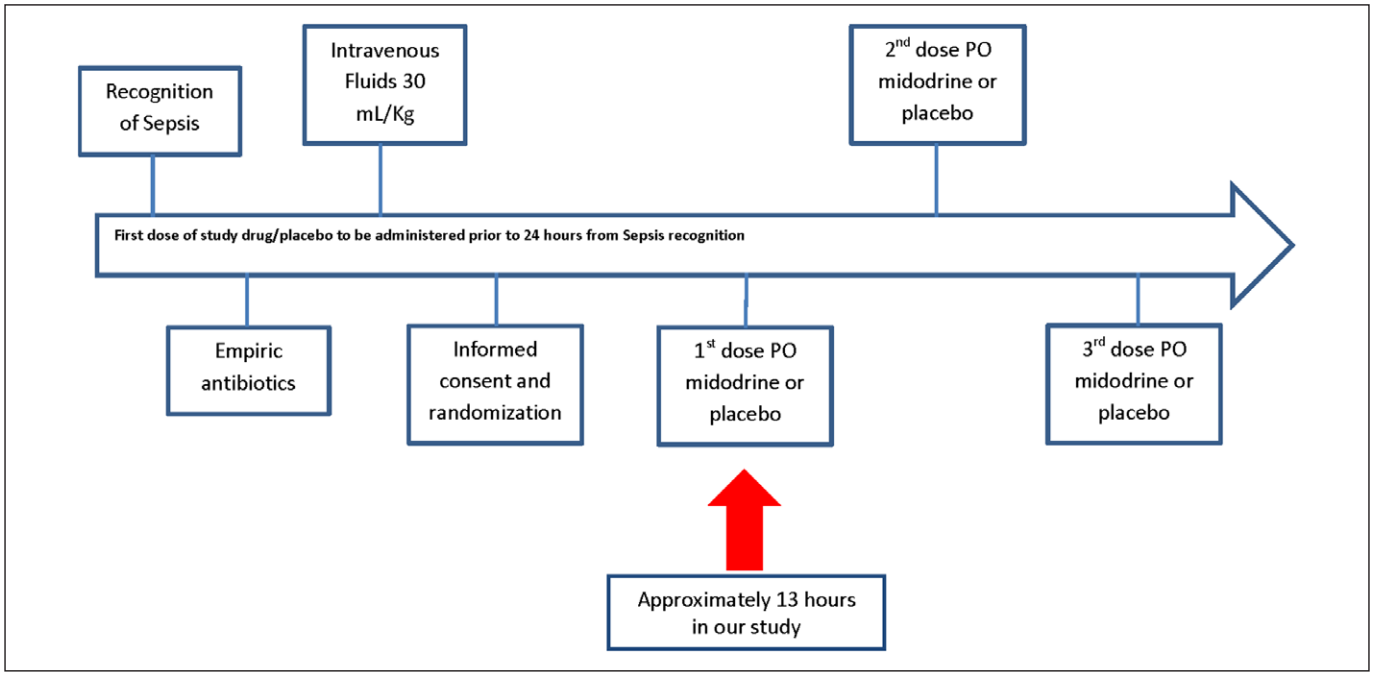

Figure 1. Timeline for recruitment and medication (midodrine vs placebo) administration. PO = per os or by mouth.

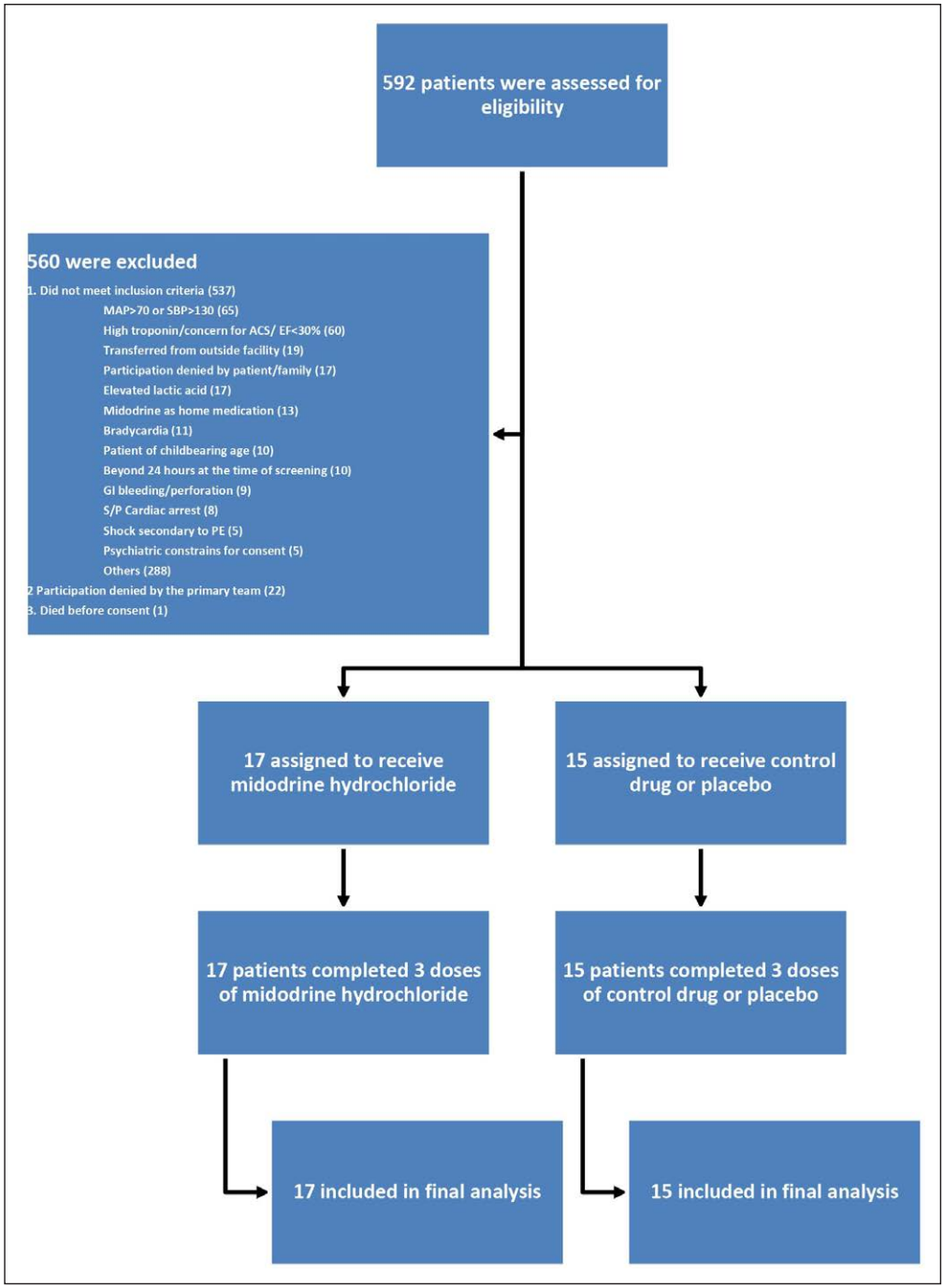

Figure 2. Screening log, eligibility, and randomization. ACS = acute coronary syndrome, EF = ejection fraction, GI = gastrointestinal, MAP = mean arterial pressure, PE = pulmonary embolism, S/P = status post, SBP = systolic blood pressure

- Bradycardia (symptomatic bradycardia with the heart rate < 40).
- Clinically recognized ischemic coronary, cerebrovascular, peripheral vascular, or intestinal event.
- Hypertension (systolic blood pressure > 160).
- Severe allergic reaction or anaphylaxis.
- Acute kidney injury, doubling of creatinine within 24 hours.
- Vomiting or gastrointestinal upset or dysuria.

Outcome Variables

The primary outcome variable was duration of IV vasopressor infusion during the first 24 hours after sepsis onset. All the vasoactive medications (vasopressin, epinephrine, phenylephrine and dopamine) were converted into norepinephrine equivalents (NEEs) to calculate the cumulative dose of NEEs. Secondary outcomes included organ failure trajectories using Sequential Organ Failure Assessment (SOFA) scores, hospital LOS, and ICU LOS. Monitoring included vital signs, vasopressor doses, and medications administered, and basic laboratory results such as renal function and lactate levels until 48 hours after midodrine administration, ICU discharge, or death. Secondary outcomes were monitored until hospital discharge. Other variables recorded and compared included demographic data (including age and gender), mechanical ventilation, concomitant administration of corticosteroids, total ICU LOS, ICU mortality, hospital LOS, hospital mortality, reinstitution of IV vasopressors after successful discontinuation (not requiring vasopressors for at least 24 hr after discontinuation), and change in creatinine value from admission to peak creatinine. Participation in the study did not result in additional laboratory testing outside of usual care.

Inclusion Criteria

All patients greater than or equal to 18 years, diagnosed with sepsis based on Sepsis-3 criteria, who were able to tolerate oral medication and able to provide consent or have a representative available to provide consent. Patients should also have had two or more blood pressure readings with MAP of less than 70 mm Hg taken at least 15 minutes apart. Prior to inclusion in the study, patients were resuscitated according to the sepsis bundle guidelines (antibiotics, fluid resuscitation with 30 mL/kg of IV fluids, lactic acid measurements, and blood cultures).

Exclusion Criteria

Patients with any of the following were excluded from the study:

- MAP greater than 70 mm Hg or systolic blood pressure greater than 130 mm Hg.
- Documented or suspected clinical or echocardiographic evidence of systolic left ventricular (LV) dysfunction (ejection fraction <30%) or cardiogenic shock.
- Elevated lactic acid levels greater than 4 mmol/L.
- Gastrointestinal bleeding.
- Clinical suspicion or confirmed diagnosis of acute intra-abdominal process (bowel obstruction, intra-abdominal sepsis, bowel ischemia, ileus).
- Inability or contraindication for oral intake (ileus, vomiting, coma, swallowing dysfunction, procedure).
- History of lactose intolerance.
- Recent myocardial infarction/concern for acute coronary syndrome/elevated troponin (within the past 3 mo).
- Current use of monoamine oxidase inhibitors.
- Recent stroke (within the past 3 mo).
- Prior use of midodrine as a home medication.
- Known allergy to midodrine.
- Comfort care measures.
- Women of child bearing age with the potential to become pregnant.
- Fludrocortisone acetate as a current home medication.
- Bradycardia (heart rate < 40).
- History of pheochromocytoma, thyrotoxicosis, peripheral vascular disease, glaucoma, or ischemic bowel disease.
- Transferred from outside facility.
- Status post cardiac arrest.
- Shock secondary to pulmonary embolism.
- Inability to consent (psychiatric/cognitive, unable to reach family).
- Study participation declined by treating physician or death before obtaining consent.

Statistical Analyses

Categorical variables are summarized as frequency (percentage). Continuous variables are presented as mean ± SD or median with interquartile range (IQR) where appropriate. Fischer exact test or chi-square test was used to compare the categorical variables and patient groups. Normally distributed continuous variables were analyzed using *t* test; nonnormally distributed data were analyzed using Wilcoxon analysis. Statistical significance was considered to be present with p value of less than 0.05. No sample size calculations are provided due to the pilot nature of this study. All statistical analyses were performed using JMP statistical software (Version 14.0; SAS Institute, Cary, NC).

RESULTS

Five-hundred ninety-two patients were screened at two study sites including Mayo Clinic, Rochester, MN, and Cleveland Clinic, Abu Dhabi from August 2017 until March 2020. The screening and patient recruitment was temporarily halted in May 2018 (for 9 mo) due to implementation of new electronic record system and was stopped at the onset of coronavirus disease 2019 pandemics (March 2020). Screening log and details of the excluded patients can be seen in Figure 2. Five-hundred sixty patients were excluded based on the exclusion criteria. Thirty-two patients were randomized into midodrine hydrochloride (n = 17) and placebo groups (n = 15). Of 592 patients screened, we were able to include only 32 patients (5.4%) as a part of this pilot study. This study was done primary to confirm the safety and feasibility of using midodrine in critically ill patients with sepsis and deliberately excluded high-risk patients with concerns of myocardial ischemia (with elevated troponin), low ejection fraction, bradycardia, and gastrointestinal bleed. Other common reason encountered for exclusion was patient's inability to consent or an impending need for a procedure which diverted patient's attention from our study.

Baseline characteristics of the patients (intervention and the placebo groups) such as gender, age, body mass index, use of antihypertensive agents, steroid use, and acuity of illness at the time of enrollment in the study (via SOFA score) are described in **Table 1**. There were no major differences in between the two groups with regard to these baseline characteristics except for serum creatinine. In addition to this, baseline heart rate, systolic and diastolic blood pressure, baseline MAP, lactic

TABLE 1.
Baseline Demographic Characteristics of the Study Cohort

Variables	Placebo ($n = 15$)	Midodrine Hydrochloride ($n = 17$)	p
Sex, *n* (%)			
Male	8 (53.3)	5 (29.4)	0.28
Female	7 (46.7)	12 (70.6)	
Age (yr), mean ± SD	70.8 ± 11.3	71.8 ± 12.6	0.71
Antihypertensive use within 7 d, *n* (%)			
Any antihypertensive	11 (73.3)	15 (88.2)	0.38
Beta blockers	6 (40.0)	8 (47.1)	
Calcium channel blocker	1 (6.6)	1 (5.8)	
Angiotensin-converting enzyme inhibitor	4 (26.7)	7 (41.2)	
Angiotensin II receptor blockers	1 (6.6)	1 (5.8)	
Thiazides	0 (0)	3 (17.6)	
Loop diuretics	8 (53.3)	5 (29.4)	
Spironolactone	2 (13.3)	1 (5.8)	
Number of patients initiated of vasopressors, *n* (%)	10 (47.6)	11 (52.4)	0.9
Corticosteroids use within 7 d of study enrollment[a], *n* (%)	1 (6.6)	3 (17.6)	–
Body mass index, mean ± SD	29.5 ± 7.1	29.1 ± 9.0	0.87
Sequential Organ Failure Assessment, mean ± SD	6.3 ± 2.6	6.8 ± 3.3	0.64
Heart rate (beats/min), mean ± SD	87 ± 15	84 ± 13	0.5
Baseline systolic BP (mm Hg), mean ± SD	101.3 ± 11.9	103.5 ± 12.4	0.61
Baseline diastolic BP (mm Hg), mean ± SD	49.5 ± 5.9	50.1 ± 7.9	0.79
Baseline mean arterial pressure (mm Hg), mean ± SD	64.8 ± 4.4	66.2 ± 8.7	0.57
Baseline lactic acid (mmol/L), mean ± SD	3.8 ± 2.1	2.6 ± 1.3	0.09
Baseline creatinine levels (mg/dL), mean ± SD	1.4 ± 0.6	2.0 ± 0.9	0.03
Mechanical ventilation at baseline, *n* (%)	1 (6.6)	1 (5.8)	1.00
Renal replacement at baseline	0	0	–

BP = blood pressure.
Dash indicates data could not be calculated.
[a]Patients taking fludrocortisone acetate as home medication were excluded.

acid, serum creatinine, need for mechanical ventilation, and renal replacement are also presented in Table 1. Both groups were similar except for higher baseline creatinine in the midodrine hydrochloride group (2.0 ± 0.9 mg/dL) compared with the placebo group (1.4 ± 0.6mg /dL) with a p value of 0.03.

Patient outcomes are delineated in **Table 2**. The median duration of IV vasopressor requirement was

TABLE 2.
Patient Outcomes

Variables	Placebo ($n = 15$)	Midodrine Hydrochloride ($n = 17$)	p
Primary outcomes			
Duration of vasopressor requirements (hr)[a]			
Median (IQR)	14 (4.1–24)	20.7 (2.3–24)	0.23
Mean ± SD	18.8 ± 7.0	14.5 ± 7.7	0.20
Secondary outcomes			
ICU LOS (d), median (IQR)	2.45 (1.6–3.2)	2.29 (1.5–3.9)	0.36
Hospital LOS (d), median (IQR)	7 (4.0–12.0)	7 (3.5–10.5)	0.41
Time from ICU admission to first dose of study dose/placebo administration (hr)	12.8	13.1	0.89
SOFA score at 24 hr of enrollment, mean ± SD	5.97 ±3.6	5.6 ± 3.7	0.78
SOFA score at 48 hr of enrollment, mean ± SD	4.1 ± 2.7	4.7 ± 3.4	0.64
SOFA score at ICU discharge, mean ± SD	4.1 ± 3.2	4.1 ± 3.1	0.98
Cumulative dose of norepinephrine equivalents (µg), mean ± SD	983 ± 1,569	729 ± 963	0.59
Number of patients requiring vasopressors for > 12 hr after first dose of study drug, *n* (%)	9 (60.0)	7 (41.2)	0.29
Cumulative urine output at 24 hr (mL), mean ± SD	1,800 ±1,072	1,631 ± 1,395	0.72
Mean arterial pressure at 24 hr (mm Hg), mean ± SD	75 ± 6.5	76 ± 7.9	0.79
Lactic acid at 24 hr (mmol/L), mean ± SD	2.4 ± 0.9	1.9 ± 1.1	0.31
Creatinine levels at 24 hr (mg/dL), mean ± SD	1.27 ± 0.6	1.4 ± 0.69	0.49
Creatinine levels at 48 hr (mg/dL), median (IQR)	1.05 ± 0.45	1.2 ± 0.63	0.48
Creatinine levels at 72 hr (mg/dL), mean ± SD	0.99 ± 0.34	1.2 ± 0.64	0.25
Need for stress dose steroids within 24 hr, *n* (%)	2 (13.3)	2 (11.8)	0.74
Duration of central catheter need (hr), mean ± SD	393.6 ± 1,051.2	95.6 ± 124.9	0.39
Duration of arterial catheter need (hr), mean ± SD	40.0 ± 16.1	58.7 ± 58.9	0.29
Any adverse events, *n* (%)	1 (6.7)	3 (17.6)	0.60

IQR = interquartile range, LOS = length of stay, SOFA = Sequential Organ Failure Assessment.
[a]For patients who were on vasopressors.

14.5 hours (SD, 8.1 hr) in the midodrine hydrochloride group compared with 18.2 hours (SD, 7.1 hr) in the placebo group, p value equals to 0.19. The intervention group needed 729 NEE (SD ± 963 NEE), compared with the placebo group which required 983 NEE (SD ± 1,569 NEE). ICU LOS was 2.29 days (IQR, 1.65–3.9 d) in the midodrine hydrochloride group at as compared to 2.45 days (IQR, 1.6–3.2 d) in the placebo group. Hospital LOS was similar in both groups with midodrine hydrochloride group at 7 days (IQR, 3.5–10.5 d) as compared to the placebo group at 7 days (IQR, 4.0-12.0 d). At 24 hours, the additional amount

IV fluid given after the initial resuscitation of 30 cc/kg was not statistically significant between the midodrine group versus the control group (1,247 mL vs 1,048 mL; $p = 0.67$). There was no difference between the groups in terms of interventions for source control and antibiotics administration for sepsis.

DISCUSSION

Our pilot study proved the feasibility of clinical trial to use oral midodrine in early sepsis. The study was not powered to detect statistically significant differences between the two groups, and therefore, the results from our study did not reach the level of statistical significance. However, a consistent trend was noted toward shorter duration of IV vasopressor requirement, shorter ICU LOS, better lactic acid clearance, and lower vasopressor (NEE) requirement overall in the first 24 hours of ICU stay for patients admitted with sepsis.

Midodrine hydrochloride has been studied in the recovery phase of shock to reduce the need for IV vasopressors through its action on alpha-1 receptors (16). It was found to reduce the need for IV vasoactive agents during the recovery phase of shock without increasing the risk for complications. Data from an observational study also support the hypothesis that the use of midodrine hydrochloride in the surgical ICU setting is associated with reduced ICU LOS and early liberation from IV vasopressors (20). Our study findings corroborate the hypothesis generated by the above studies. However, the design of our study had the advantage of introducing therapy in the early phase of sepsis rather than the recovery phase, thereby shortening the stay in the ICU. This study also demonstrated that midodrine hydrochloride can reduce the need for IV vasoactive agents in the early phase of sepsis rather than the recovery phase of shock. The prospective design of the study and blinded randomization also negated the disadvantages of allocation and selection bias. It also minimized the statistical unreliability from confounding factors. Recent study from Santer et al (27) evaluated the use of midodrine in a heterogeneous patient population for hypotension. Majority of the patient subset in that study included postoperative cardiothoracic patients who are expected to have hypotension for various other causes. Other shortcomings of their study included high dose of vasopressor requirement at the time of enrollment and extended need for vasopressors. A crucial point to take away from our study is that the right patient selection is the key for appropriate use of midodrine for hypotension. Our goal is simple, to reduce the need of vasopressor use to less than 24 hours, in low-risk patients, so that the patients can possibly avoid the need for central venous catheter placement or even an ICU admission.

Midodrine has been shown to be effective in the elderly population for management of orthostatic hypotension and syncope (28). It has also been effective in avoiding hypotension in patients during dialysis (29). The underlying mechanism that supports its use is vasoconstriction of both the arterial and venous vascular beds (30, 31). It is widely accepted that hypotension in sepsis (septic shock) is largely secondary to peripheral vasodilatation, with myocardial dysfunction as a minor contributor (32, 33). In theory, the vasoconstrictive effects of midodrine hydrochloride should mitigate the vasodilatory effects of sepsis and septic shock. As such, it can potentially improve organ perfusion and reduce organ dysfunction, in the same manner as IV vasopressors by maintaining physiologically appropriate MAP. This effect is crucial for end organ perfusion especially to the kidneys, which can potentially decrease incidence of renal failure in critically ill patients. It can also potentially decrease need for aggressive administration of IV fluids, which can decrease fluid overload and its downstream consequences (34). In addition, if it can decrease the need for IV vasopressor agents; patients can avoid risks and discomfort associated with central catheter placement. Shorter duration of need for a central venous access can also reduce the morbidity associated with central catheter–associated blood stream infections. Our pilot study showed that the intervention group had a much shorter time of central venous access need as compared to the control group (Table 2).

From an economic perspective, ICU admissions carry significant financial burden. The average cost of an ICU admission can range from $3,300 to $28,100 USD per patient or higher, depending on patient age and additional medical comorbidities (35–37). The costs incurred during an ICU admission is in part contributed by the length of ICU stay, individualized interventions, and procedures such as central venous catheters and medications including IV vasopressors.

Complications related to these invasive procedures incur an additional cost and inconvenience to the patients and to the healthcare system at a different level. Literature supports the fact that "day 1" of the ICU stay is the most resource intensive compared with the succeeding days (38). Appropriate identification and management in the early hours of sepsis is a key determinant for the trajectory for the rest of the disease course in the ICU (39, 40). In our study, we intended to interject early in the course of sepsis, with an intervention during these early hours. With the use of midodrine hydrochloride in this patient population, we were able to successfully show a trend of reduced vasopressor requirement (time duration and cumulative dose in terms of NEEs), thereby altering the clinical trajectory.

From a safety perspective, the use of midodrine hydrochloride was not associated with serious AEs in either of the groups. The small sample size of this pilot study prevents accurate estimation of the rate of AEs. Despite the feared cardiovascular side effects of sinus bradycardia with midodrine, it has been successfully used for the treatment of stunned myocardial with improved perfusion and benefit in improving hypotension (21). Furthermore with the recently evolving evidence highlighting association of high dose midodrine (20 mg, 3 times daily) with bradycardia, our choice of modest dosing (10 mg, 3 times daily) seems more appropriate (27).

Limitations of our study include the small sample size of the intervention and control groups. Our study does not allow us to comment about the safety or benefit of using midodrine in subset of patients with reduced LV ejection fraction (excluded from our study group). Another limitation of our study was a low inclusion rate, but this can also be viewed as strength and platform for future studies that midodrine is effective for a selective group of patients in the ICU. To establish the safety and feasibility of using midodrine in critically ill patients with sepsis, we intentionally designed a stringent inclusion and exclusion criteria (as explained in the previous sections) which resulted in a large set of screened patients to be excluded from the study. Other common reason encountered for exclusion was patient's inability to consent or an impending need for a procedure (common occurrence in the ICU) which diverted patient's attention from our study. A significant proportion of patients in ICU with septic shock have a component of sepsis induced cardiomyopathy, with an associated drop in LV ejection fraction, this was also seen in our ICU population during the screening phase (41, 42). Occasionally, we also encountered critical care physicians who were not convinced with the safety and utility of midodrine in patients with sepsis.

In conclusion, this pilot, placebo-controlled clinical trial confirmed the feasibility of studying midodrine as vasopressor sparing agent in early sepsis. There were no significant AEs, and although not statistically significant, duration of vasopressors was lower in midodrine group. The results generated from this study lay the groundwork for the future phase II randomized control trials.

1 *Department of Medicine, Division of Pulmonary and Critical Care Medicine, Multidisciplinary Epidemiology and Translational Research in Intensive Care Group (METRIC), Mayo Clinic, Rochester, MN.*

2 *Department of Cardiovascular Medicine, Warren Alpert School of Medicine at Brown University, Providence, RI.*

3 *Department of Medicine, Division of Pulmonary and Critical Care Medicine, Weill Cornell Medical College, Doha, Qatar.*

4 *Multidisciplinary Epidemiology and Translational Research in Intensive Care Group (METRIC), Mayo Clinic, Rochester, MN.*

5 *Critical Care Medicine, Mayo Clinic Health System, La Crosse, WI.*

6 *Critical Care Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates.*

7 *Department of Anesthesiology and Perioperative Medicine, Division of Critical Care, Multidisciplinary Epidemiology and Translational Research in Intensive Care Group (METRIC), Mayo Clinic, Rochester, MN.*

8 *Department of Medicine, Division of Pulmonary and Critical Care Medicine, Multidisciplinary Epidemiology and Translational Research in Intensive Care Group (METRIC), Mayo Clinic, Rochester, MN.*

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For information regarding this article, E-mail: Lal.Amos@mayo.edu; manavamos@gmail.com

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