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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should midodrine be used as an intravenous vasopressor-sparing agent in septic shock?

A 55-year-old male presents to the emergency department with dysuria, fevers, and chills. His temperature is 38.3°C (101.8°F), blood pressure 75/46 mm Hg, and heart rate 113 beats per minute. Laboratory test results show a white blood cell count of 17.0 × 10^9/L (reference range 4.5–11.0) and serum lactate 4 mmol/L (> 2). Urinalysis shows 50 to 100 white blood cells per high-power field (0–3), as well as nitrites and leukocyte esterase. He is given 3 L intravenous fluids and is started on intravenous meropenem. Two hours later, his blood pressure is 81/50 mm Hg. Should we use midodrine rather than an intravenous vasopressor (IVP) for blood pressure support in this patient with septic shock?

A: No. While some research suggests that midodrine may be used to wean down IVPs in select patients during the recovery phase of septic shock, there are no robust data to suggest that midodrine can be used to avoid or delay IVP therapy or intensive care unit (ICU) admission in patients with septic shock in intermediate-care or general medicine hospital units.

SEPTIC SHOCK

Septic shock is defined as "a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality,"[1] and is clinically recognized by persistent hypotension, hyperlactatemia (often serum lactate > 2 mmol/L), and the need for IVPs to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher.[1]

The epidemiology of septic shock has been historically difficult to study, but studies have estimated that sepsis affects approximately 1.7 million adults annually in the United States and is present is 30% to 50% of hospitalizations that result in death.[2,3] Mortality rates for septic shock have been estimated to be at least as high as 41%.[4] Current standard-of-care treatment for septic shock includes fluid resuscitation, antimicrobials, IVPs to maintain an MAP of 65 or higher, and intravenous corticosteroids if there is an ongoing requirement for multiple vasopressors.[5]

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WHY ALL THE INTEREST IN MIDODRINE?

Many of the treatments for septic shock require a higher level of care and more frequent monitoring in the ICU, which results in increased use of healthcare resources and increased costs. Thus, hospitalists and intensivists have been interested in IVP-sparing therapies for septic shock to improve both clinical and economic outcomes. Midodrine, an oral alpha-1 adrenergic receptor agonist with US Food and Drug Administration approval for symptomatic hypotension, produces a predictable, dose-dependent increase in blood pressure.[6] Midodrine has favorable pharmacodynamic and pharmacokinetic characteristics, with rapid absorption following oral administration,[6] and approximately 93% bioavailability.[7] Additionally, side effects are minimal, most notably paresthesia, piloerection, shivering, bradycardia, and urinary retention.[8]

WHAT DO THE DATA SHOW?

Only a few studies have addressed our question. A placebo-controlled, double-blind, randomized pilot trial conducted in 2 medical ICUs recruited adult patients hospitalized with sepsis who had an MAP of less than

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TABLE 1
Studies of midodrine in the treatment of septic shock

Authors	Study design	Patient population	Outcomes
Lal et al[9]	Pilot, placebo-controlled, double-blind, randomized trial	Adult medical ICU patients hospitalized with sepsis; mean arterial pressure < 70 mm Hg despite sepsis treatment	Decreased duration of IVPs (P = .19) Decreased total IVP requirement (P = .59) Shorter ICU length of stay (P = .36) Similar hospital length of stay (P = .41)
Whitson et al[7]	Single-center retrospective cohort study	Patients hospitalized with septic shock requiring at least 24 hours of IVPs who demonstrated a period of clinical stability	Decreased IVP duration (P < .001) Decreased ICU length of stay (P = .017) Reduction in total IVP days and ICU patient days over year of study
Adly et al[10]	Single-center retrospective control study	Resuscitated patients with septic shock who demonstrated clinical stability on low-dose IVP for at least 24 hours	Reduced IVP (norepinephrine) duration (P = .001) Shorter IVP weaning period in septic shock recovery phase (P < .001) Decreased mortality (43.3% vs 73.3%, P = .018)
Santer et al[11]	Randomized, double-blind, placebo-controlled trial	Hypotensive adult patients on single-agent IVP unable to be weaned from IVPs for at least 24 hours	No difference in time to IVP discontinuation (23.5 vs 22.5, P = .62) No difference in ICU length of stay (6 days vs 6 days, P = .46) No difference in time to ICU discharge readiness (5 days vs 5 days, P = .64) No difference in ICU readmission rate (1.5% vs 4.5%, P = .62) Increased rates of bradycardia (7.6% vs 0%)

ICU = intensive care unit; IVP = intravenous vasopressor

70 mm Hg despite receiving antibiotics and sepsis-dose fluids (30 mL/kg crystalloids).[9] Patients in the intervention group (n = 17) received a total of 3 doses of oral midodrine 10 mg every 8 hours in addition to the usual sepsis care, including subsequent initiation of IVPs. The study reported a decreased median duration of IVPs in the midodrine group, decreased total IVP requirement in the first 24 hours of ICU stay, and shorter ICU length of stay when compared with the standard-of-care cohort.[9]

The results of the study were not significant, but the study was not powered to detect statistically significant differences between the groups. Thus, it could not be concluded that midodrine can be used in early treatment of septic shock or that it is associated with improved outcomes. However, the study did prove the feasibility of conducting a large clinical trial to study the use of oral midodrine in early sepsis.[9]

Whitson et al[7] investigated a similar clinical scenario and conducted a single-center retrospective cohort study to describe the feasibility and utility of oral midodrine to replace IVPs in the recovery phase of septic shock. The investigators identified patients admitted with septic shock who had already received at least 24 hours of IVPs and were demonstrating clinical stability as evidenced by stable or decreasing doses of IVPs. The clinical team administered midodrine concurrently with IVPs in select patients, and doses of midodrine were incrementally increased until IVPs were no longer needed. Importantly, the administration, dosing, and tapering of midodrine were made on an individual-patient basis and were not protocol-driven. In the patients who received midodrine with IVPs, the study found a 24% decrease in IVP duration and a 20% decrease in ICU length of stay, as well as a reduction of 121.5 total IVP days and 222.3 ICU patient days over the year that the study lasted.[7]

Adly et al[10] similarly conducted a prospective controlled study in septic shock patients who demonstrated clinical stability on low-dose IVPs for at least

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24 hours.[10] Select patients were randomized to receive midodrine 10 mg three times daily in addition to IVPs, and the investigators reported decreased IVP duration, shorter IVP weaning time, and decreased mortality risk in the intervention group.[10] However, this study was unblinded and did not have enough power to detect a true difference with the use of midodrine.

The MIDAS (Effect of Midodrine vs Placebo on Time to Vasopressor Discontinuation in Patients With Persistent Hypotension in the Intensive Care Unit) trial[11] is the largest randomized clinical trial to date investigating midodrine as an adjunct to standard treatment in shortening the duration of IVP requirement for patients with vasodilatory shock in the ICU. This study recruited 132 hypotensive adult patients on single-agent IVP treatment who were unable to be weaned from IVPs for at least 24 hours; 66 patients received oral midodrine every 8 hours in addition to standard of care treatment. The investigators found no significant difference between the intervention and placebo groups in time to discontinuation of IVPs, time to ICU discharge readiness, or ICU or hospital length of stay. Bradycardia was an adverse event significantly more common in the midodrine group.[11]

Table 1 summarizes findings of the studies discussed here.[7,9,10,11]

THE BOTTOM LINE

Research and robust data are lacking regarding the use of midodrine as an adjunctive IVP-sparing treatment option in septic shock. Most studies have evaluated midodrine in the recovery phase of shock. A major limitation of many of these studies is that midodrine was administered every 8 hours, while its half-life is shorter at 3 to 4 hours, resulting in large swings in plasma concentrations of the medication and limiting confidence in these trials, both positive and negative.

Though midodrine has few side effects and is relatively safe, it should not be used in septic shock treatment to delay ICU admission or IVP initiation. Oral midodrine may be used to wean IVPs in select patients with septic shock already in the ICU, though the characteristics of patients who may benefit from midodrine are not quite clear. There is no definitive evidence that midodrine is effective for the treatment of hypotension in critically ill patients.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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