Putting midodrine on the MAP: An approach to liberation from intravenous vasopressors in vasodilatory shock

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Purpose. Prolonged duration of intravenous (IV) vasopressor dependence in critically ill adult patients with vasodilatory shock results in increased length of stay in both the intensive care unit (ICU) and hospital, translating to higher risk of infection, delirium, immobility, and cost. Acceleration of vasopressor liberation can aid in reducing these risks. Midodrine is an oral α_1-adrenergic receptor agonist that offers a potential means of liberating patients from IV vasopressor therapy. This clinical review summarizes primary literature and proposes a clinical application for midodrine in the recovery phase of vasodilatory shock.

Summary. Five studies with a total of over 1,000 patients conducted between 2011 and 2021 were identified. In observational studies, midodrine administration was demonstrated to lead to faster time to liberation from IV vasopressor therapy and shorter ICU length of stay in patients recovering from vasodilatory shock. These findings were not replicated in a prospective, multicenter, randomized controlled trial. In this review, literature evaluating midodrine use for IV vasopressor liberation is summarized and study limitations are discussed.

Conclusion. On the basis of this review of current literature, recommendations are provided on selecting appropriate candidates for adjunctive midodrine in the recovery phase of vasodilatory shock and considerations are discussed for safely and effectively initiating, titrating, and discontinuing therapy.

Keywords: drug liberation, intensive care units, midodrine, shock, vasoconstrictor agents

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Vasodilatory shock is the most common form of shock encountered in an intensive care unit (ICU) setting, accounting for over 60% of all shock cases.[1,2] The mainstay of treatment for vasodilatory shock is a combination of fluid resuscitation and continuous infusion of intravenous (IV) vasopressor therapy. Once the patient is hemodynamically optimized, liberation from IV vasoactive therapy commences by way of weaning from vasopressors. This is commonly referred to as the recovery phase of shock.

Some patients are difficult to wean from vasopressors due to adrenal insufficiency, hypovolemia, or persistent vasodilation.[3] In the cases of adrenal insufficiency or recurrent hypovolemia, the underlying cause should be corrected by administration of corticosteroids and IV fluid boluses, respectively.[3,4] For patients with persistent vasodilation, IV vasopressors continue to be the mainstay of treatment.

Vasopressors are not benign medications and carry a plethora of adverse effects, including depressed cardiac output, acute kidney injury, tachyarrhythmias, lactic acidosis, hyperglycemia, and peripheral, myocardial, and intestinal ischemia.[1,5,6] Patients may also experience indirect adverse effects related to the

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administration of IV vasopressors, for example, from the drug diluent or from access devices used for drug administration. The fluid that serves as a vehicle for IV vasoactive agents may contribute to volume overload, hyperchloremia, or hyperglycemia depending on the diluent composition.[7-10] Central venous access is preferred for safe delivery of IV vasopressor therapy, but such access can also induce harm, including vascular, cardiac, and pulmonary complications.[11] Prolonged use of central access devices is further associated with risk of device dysfunction and infection.[12] The inability to liberate patients from IV vasopressors also prolongs ICU length of stay (LOS).[13]

KEY POINTS

- Midodrine is an oral α_1-adrenergice receptor agonist with a potential role in liberating patients from intravenous vasopressors.
- Five studies evaluating this therapeutic use of midodrine in over 1,000 patients between 2011 and 2021 are reviewed.
- Adjunctive midodrine is recommended during the recovery phase of vasodilatory shock with a starting dose of 20 mg every 8 hours and titration to patient response.

Drug overview

Midodrine is an oral prodrug that increases blood pressure via activation of α_1-adrenergic receptors in the vasculature. It is available as 2.5-mg, 5-mg, and 10-mg tablets. Midodrine is approved by the Food and Drug Administration for symptomatic orthostatic hypotension, dosed at 10 mg 3 times daily with a recommended maximum daily dose of 30 mg.[14] One hour following oral administration of midodrine 10 mg, standing systolic blood pressure increases by 15 to 30 mm Hg.[15] Off-label uses include refractory ascites, prevention of hemodialysis-induced hypotension, hepatorenal syndrome, and vasovagal syncope.[13] The sympathomimetic effect of midodrine was first noted in a 1979 German study, where midodrine was compared to the adrenergic drug etilefrine.[16] In this study of 120 children with a variety of infectious diseases, midodrine was concluded to be a safe and effective medication to treat hypotension due to infection. Adverse effects from midodrine are due to its α_1 agonist properties and include supine hypertension, piloerection, chills, paresthesias, and urinary retention.[14,15] Reflex bradycardia, although uncommon, may also occur due to increased systemic vascular resistance, because cardiac β-adrenergic receptors are not affected by midodrine directly.[17]

Midodrine has 93% oral bioavailability and undergoes hepatic deglycination to its active metabolite, desglymidodrine. Desglymidodrine reaches peak serum concentrations 1 to 2 hours after administration and has a plasma half-life of 3 to 4 hours with minimal protein binding. It is primarily (80%) eliminated in the urine by active tubular secretion. For patients with renal dysfunction receiving midodrine for orthostatic hypotension or secondary hypotensive disorders, it is recommended to initiate therapy at a lower dose of 2.5 mg to reduce the risk of blood pressure that is higher than desired.[14]

With its clinical effect of increasing blood pressure, midodrine offers a potential means of liberating patients from IV vasopressor therapy. The purpose of this clinical review is to summarize primary literature related to midodrine as an adjunctive therapy for vasopressor liberation and to propose a clinical application for midodrine in the recovery phase of vasodilatory shock.

Review of the literature

A narrative review was conducted of the literature related to use of midodrine as an adjunct for vasopressor liberation. Literature to include in this review was identified using a PubMed search with the Medical Subject Headings (MeSH) terms "intensive care unit" and "midodrine" and filtered by publication date (2011 through 2021) and language (English). Fifteen articles were initially identified. Literature for this narrative review was included if study patients were admitted to the ICU receiving one or more vasopressors for vasodilatory shock and midodrine was administered. Outcomes of interest were IV vasopressor duration, hospital and ICU LOS, hemodynamic changes, and adverse effects due to midodrine administration. Commentaries (n = 5), review articles (n = 3), and articles that did not report on outcomes of interest (n = 2) were not reviewed. Five studies, with a total of over 1,000 patients, evaluated the use of midodrine as a means to liberate patients from IV vasopressors and were included in this review (Table 1).

Observational studies. The earliest study was a single-center, prospective, observational study published in 2013 by Levine et al[18] that included 20 adult surgical ICU patients who received IV vasopressors and at least 3 doses of midodrine and required ongoing ICU admission only for the administration of vasopressors. Patients had a mean Acute Physiologic and Chronic Health Evaluation (APACHE) II score of 18 (SD, 6) and were on vasopressors for a median of 3 days before initiation of midodrine. The most frequent dosing strategy for midodrine was 20 mg 3 times daily (range, 5-20 mg 3 times daily). The primary outcome was the degree of change in IV vasopressor infusion rate from 12 hours before midodrine administration to 4 hours after the fourth dose, expressed in phenylephrine equivalents. The mean initial phenylephrine equivalent rate before the first midodrine dose was 41.0 (SD, 33.4) μg/min. The mean rate of decline in vasopressor infusion rate changed from –0.62 (SD, 1.4) μg/min/h phenylephrine equivalents before midodrine administration to –2.20 (SD, 2.45) μg/min/h phenylephrine equivalents with the first 4 doses of midodrine

($P = 0.012$). The decline in vasopressor infusion rate was over 3 times faster after the addition of midodrine and this difference was statistically significant, suggesting that midodrine is an effective adjunctive agent to decrease vasopressor requirements. Within 1 day, 14 (70%) of the patients had been liberated from IV vasopressors. Mean arterial pressure (MAP) and heart rate were not significantly different before and after midodrine administration

Table 1. Summary of Literature

Parameter	Levine et al (2013)[18]	Whitson et al (2016)[19]	Poveromo et al (2016)[20]	Rizvi et al (2018)[21]	Santer et al (2020) (MIDAS)[22]
Design	Prospective, observational	Retrospective, observational	Retrospective, observational	Retrospective, observational	Prospective, multicenter RCT
Sample size	*n* = 20	*n* = 175	*n* = 188	*n* = 1,119 (663 receiving VP)	*n* = 132
Comparator	NA	VP alone (*n* = 140) vs VP/midodrine (*n* = 135)	VP alone (*n* = 94) vs VP/midodrine (*n* = 94)	NA	Midodrine (*n* = 66) vs placebo (*n* = 66)
Inclusion criteria	Admitted to surgical ICU, received VP and at least 3 doses of midodrine, and remained in ICU only for dependence on VP	Admitted to medical ICU with septic shock, required at least 24 hours of VP therapy, and had stable or decreasing doses of VP	Admitted to cardiovascular, medical/surgical, or neuro/trauma ICU and received VP for 2+ hours for hypotension secondary to cardiovascular, trauma or sepsis diagnoses	Admitted to any ICU (surgical, medical, neurological) and initiated on off-label midodrine	Admitted to surgical or medical ICU, was hypotensive, and required VP for at least 24 hours
Exclusion criteria	• Preadmission midodrine use • Hypotension due to hypovolemia or adrenal insufficiency • History of orthostatic hypotension	• None listed	• Died within 24 hours of ICU admission • Midodrine for indication other than VP weaning • Received fewer than 3 doses of midodrine	• Midodrine initiated outside of ICU • Preadmission midodrine use	• Hypoperfusion, liver or kidney failure, hypovolemic shock, thyrotoxicosis, severe heart disease, pheochromocytoma, acute urinary retention, or bradycardia
Severity of illness	APACHE II: 18	APACHE IV: 84 vs 83	APACHE IV: 82 vs 59 ($P = 0.02$)	APACHE III: 78	APACHE II: 15 vs 15
Midodrine dosing	Mode: 20 mg 3 times daily; range: 5-20 mg 3 times daily	Average: 19 mg every 8 hours; initiation: 10 mg every 8 hours; max: 40 mg every 8 hours	Mode: 10 mg 3 times daily; range: 2.5-10 mg 2-6 times daily	Not stated	Fixed: 20 mg every 8 hours
Efficacy	• Rate of decline of VP infusion rate changed from –0.62 μg/min/h phenylephrine equivalents before midodrine to –2.2 μg/min/h with midodrine • 70% of patients were discontinued from IV VP within 1 day	• Decreased VP duration (3.8 vs 2.9 days, $P < 0.001$) • Decreased ICU LOS (9.4 vs 7.5 days, $P = 0.017$)	• VP discontinued 1.2 days after midodrine • Shorter time to ICU discharge after discontinuation of VP (1.5 vs 0.8 days, $P = 0.01$) • No difference in ICU LOS ($P = 0.29$)	• 48% discontinued from VP within 24 hours of midodrine initiation • Median VP infusion rate decreased significantly from baseline to 24 hours ($P = 0.002$)	• No difference in time to VP discontinuation (24 vs 23 hours, $P = 0.62$) • No difference in ICU discharge readiness or ICU/hospital LOS • VP discontinued 18.4 hours earlier in post hoc analysis of subgroup receiving epidural analgesia ($P = 0.045$)

Table 1. Continued

Parameter	Levine et al (2013)[18]	Whitson et al (2016)[19]	Poveromo et al (2016)[20]	Rizvi et al (2018)[21]	Santer et al (2020) (MIDAS)[22]
Safety	• No clinically concerning adverse effects • Midodrine discontinued prematurely in 2 patients	• Midodrine discontinued prematurely in 1 patient due to bradycardia	• Within 24 hours of starting midodrine, 6.4% had hypertension and 12.8% had new-onset bradycardia	• 15% incidence of bradycardia • 0.18% incidence of ischemic bowel	• No difference in rate of hypertension (10.6% vs 7.6%) • Increased rate of bradycardia (7.6% vs 0%, $P = 0.02$)
Conclusion	Midodrine increased the speed of VP weaning.	Midodrine reduced VP duration and ICU LOS in patients recovering from septic shock.	Midodrine resulted in shorter time to ICU discharge after discontinuation of VP.	Nearly half of patients were able to discontinue VP within 24 hours of initiating midodrine.	Midodrine did not decrease time on VP or ICU LOS, expect in a post hoc subgroup analysis.
Limitations	• Single center • Observational • Small sample size • Limited to surgical patients • Clinical outcomes not assessed • Lack of comparator group	• Single center • Observational • Relatively small sample size	• Single center • Observational • Relatively small sample size • Significant baseline differences between groups • Unclear clinical relevance of "significant" findings	• Single center • Observational • Lack of comparator group • Midodrine doses not reported	• Relatively small sample size • Heterogeneous cohort may have limited findings • Lack of midodrine titration • Subgroup analysis not specified a priori

Abbreviations: APACHE, Acute Physiologic and Chronic Health Evaluation; ICU, intensive care unit; LOS, length of stay; NA, not applicable; RCT, randomized controlled trial; VP, vasopressors.

($P = 0.69$ and $P = 0.66$, respectively). No patients experienced clinically concerning hypertension or other serious adverse effects. Midodrine was discontinued before weaning from vasopressors in 2 patients, one with postoperative bleeding who required return to the operating room and was later reinitiated on midodrine and the other with acute hypotension due to intra-abdominal bleeding who died.

Results from this study suggest that midodrine is effective in increasing the speed of vasopressor weaning and thus may decrease the duration of vasopressors without hemodynamic compromise. However, the patients included in this study were in the surgical ICU and had a mean APACHE II score of 18 (estimated mortality rate of 12% in postoperative patients), indicating that they may not be as high risk as other critically ill patients. Notably, the study did not evaluate potentially relevant clinical outcomes such as mortality, ICU LOS, and vasopressor-free days and did not discuss a strategy for subsequent discontinuation of midodrine.

A single-center, retrospective, observational study published in 2016 by Whitson et al[19] assessed 275 medically critically ill adults with septic shock who had stable or decreased doses of vasopressors after at least 24 hours of vasopressor support. Patients who received IV vasopressors only ($n = 140$) were compared to those who received IV vasopressors and oral midodrine ($n = 135$). Patients in the 2 groups had similar APACHE IV scores (84 vs 83, $P = 0.55$), rates of mechanical ventilation (76% vs 68%, $P = 0.21$), and rates of corticosteroid administration (29% vs 26%, $P = 0.72$). The mean vasopressor dose at the time of midodrine initiation was 0.09 μg/kg/min for 97 patients receiving norepinephrine and 0.77 μg/kg/min for 38 patients receiving phenylephrine. Midodrine was started at a standard dose of 10 mg every 8 hours that was increased incrementally through a nonprotocolized approach to a maximum dose of 40 mg every 8 hours. The average dose of midodrine required to wean patients from vasopressors was 18.7 (SD, 9.6) mg every 8 hours. Primary outcome measures included duration of IV vasopressor administration and ICU LOS. The mean vasopressor duration was reduced by 1 day with adjunctive midodrine (3.8 vs 2.9 days, $P < 0.001$), and ICU LOS was reduced by 20% (9.4 vs 7.5 days, $P = 0.017$). Fewer patients in the midodrine group required reinitiation of IV vasopressors. Midodrine was stopped prematurely in one patient due to secondary bradycardia, which resolved without further intervention. No other complications of midodrine were reported.

The findings from this study suggest that midodrine could be an effective adjunct to reduce IV vasopressor duration and ICU LOS in patients

recovering from septic shock. Benefits were observed with an average dose of about 20 mg every 8 hours, similar to that reported by Levine et al,[18] although doses up to 40 mg every 8 hours were allowed. In a letter to the editor, use of the mean, as opposed to the median, for reporting ICU LOS and APACHE IV scores was questioned.[23] Whitson et al[24] responded with new data, reporting a median ICU LOS of 8 days in the vasopressor-only group compared to 4 days in the vasopressor-midodrine group ($P = 0.017$). The median APACHE IV scores were 83 and 77.5 in the 2 groups, respectively ($P = 0.55$). These results confirmed the authors' initial findings that addition of midodrine was associated with a significant reduction in ICU LOS in patients recovering from septic shock.

Also in 2016, Poveromo et al[20] reported a single-center retrospective study of 188 critically ill adults representing cardiovascular, medical, surgical, neurological, and trauma ICU patients who received vasopressors alone ($n = 94$) or vasopressors and midodrine ($n = 94$). Patients were included in the study if they received one or more IV vasopressors for at least 2 hours and had an etiology of hypotension related to cardiovascular, trauma, or sepsis diagnoses. Patients were assigned to the combination cohort if they received at least 3 doses of midodrine. At baseline, patients in the vasopressor-only group had a higher median APACHE IV score (82 vs 59, $P = 0.02$), were less likely to receive corticosteroids (40% vs 55%, $P = 0.04$), and were less likely to receive 2 or more vasopressors (37% vs 60%, $P < 0.01$). Midodrine was initiated and titrated at the discretion of individual prescribers. The modal dose of midodrine was 10 mg 3 times daily (range, 2.5-10 mg 2-6 times daily), and midodrine was continued for a median duration of 4.4 days (interquartile range [IQR], 3.2-7.8 days). The primary outcome was the time to IV vasopressor discontinuation after initiation of midodrine, which was 1.2 days (IQR, 0.5-2.8 days). Compared to patients receiving vasopressor alone, those also receiving midodrine had a shorter time to ICU discharge after discontinuation of IV vasopressor therapy (1.5 vs 0.8 days, $P = 0.01$), but there was no difference between the groups in ICU LOS ($P = 0.29$) and the midodrine group had a longer hospital LOS (9.5 vs 12 days, $P < 0.01$). Forty percent of patients in the midodrine group required reinitiation of vasopressors while the patient was on midodrine, but only 4% required reinitiation of vasopressors after midodrine was discontinued. During the first 24 hours after midodrine initiation, 6 patients (6.4%) experienced hypertension and 12 patients (12.8%) experienced new-onset bradycardia.

This study evaluated a more diverse group of ICU patients and demonstrated a shorter time to ICU discharge after vasopressor discontinuation with the use of adjunctive midodrine; however, interpretation of the results is severely limited by significant differences in baseline characteristics between the study groups. Furthermore, the high rate of vasopressor reinitiation is concerning, the primary outcome was assessed only in the study group, and other clinically relevant outcomes such as vasopressor-free days were not reported.

With prior research focused on observational studies of small patient cohorts, Rizvi et al[21] published a much larger report of 1,119 surgical, medical, and neurological ICU patients who received midodrine for treatment of hypotension between 2011 and 2016. All adult patients for whom midodrine was initiated in the ICU (who were not receiving it at home) were included and represented patients on IV vasopressors at baseline ($n = 663$) and patients not receiving IV vasopressors ($n = 456$). The subgroup receiving IV vasopressors at baseline had a median APACHE III score of 78, an ICU LOS of 6 days, and a hospital mortality rate of 19%. Vasopressors were discontinued for nearly half of the patients (319 of 663) 24 hours after initiation of midodrine. For patients remaining on vasopressors at 24 hours, the median infusion rate was significantly lower than at baseline (immediately before midodrine initiation), although the clinical significance of this is questionable as the absolute values were similar (baseline: 19.9 μg/min; IQR, 5.1-27.8 μg/min; 24 hours: 19.9 μg/min; IQR, 4.9-27.8 μg/min; $P = 0.002$). Bradycardia occurred in 15% of patients receiving midodrine, while ischemic bowel occurred in 2 patients (0.18%).

This study provided a perspective on midodrine use in a large cohort of diverse patients and demonstrated a clinically relevant change in the proportion of patients requiring IV vasopressors 24 hours after midodrine initiation. The lack of response to midodrine exhibited by some patients may suggest the existence of midodrine responders and nonresponders, a hypothesis that requires further investigation. Interpretation of the study results is limited by the lack of a control group. Additionally, midodrine was initiated, titrated, and discontinued at the discretion of the clinical team through a nonprotocolized approach, and the dose and duration of midodrine administered were not reported.

Randomized controlled trial. The MIDAS trial, published in 2020, was an international, prospective, multicenter, double-blind, placebo-controlled trial that enrolled critically ill, hypotensive patients for whom use of an IV vasopressor was required for at least 24 hours.[22] Patients with inadequate tissue perfusion, liver failure, renal failure, hypovolemic shock, thyrotoxicosis, severe heart disease, pheochromocytoma, acute urinary retention, and bradycardia were excluded. The study included 132 patients randomized 1 to 1 to receive a fixed 20-mg dose of midodrine or placebo 3 times daily until IV vasopressors were stopped, the patient was discharged from the ICU, or an adverse event occurred. Adverse events were defined as worsening hypotension requiring high-dose vasopressors (>100 μg/min phenylephrine, >60 μg/min metaraminol, or >8 μg/min norepinephrine), signs and symptoms of

organ failure or tissue hypoperfusion requiring epinephrine administration at any dose, or drug-related adverse effects. The primary outcome was time, in hours, from initiation of midodrine or placebo until IV vasopressor discontinuation. "Discontinuation" was defined as a vasopressor-free period of at least 24 hours during which blood pressure goals were maintained. Secondary outcomes included hospital and ICU LOS, ICU readmission rate, and adverse events.

Reasons for ICU admission in the midodrine and control groups, respectively, included surgical (68% vs 64%), sepsis (20% vs 20%), and other (12% vs 17%) medical reasons. The APACHE II score (14.7 vs 14.8), duration of vasopressors before study drug administration (35.5 vs 35.4 hours), and vasopressor dose at enrollment were similar between the groups. There was no difference in time to IV vasopressor discontinuation with midodrine compared to placebo (midodrine: median, 23.5 hours; IQR, 10-54 hours; placebo: median, 22.5 hours; IQR, 10.4-40 hours; $P = 0.62$). There was also no difference in time to ICU discharge readiness (5 vs 5 days, $P = 0.64$), ICU LOS (6 vs 6 days, $P = 0.46$), or hospital LOS (11 vs 14 days, $P = 0.45$). Hypertension occurred at a similar rate in both groups, while bradycardia occurred more frequently with midodrine (7.6% vs 0%, $P = 0.02$). In a post hoc subgroup analysis, there was a significant difference in time to IV vasopressor discontinuation when midodrine was administered to patients receiving epidural analgesia. Among the 23% of patients who received epidural analgesia, the time to vasopressor discontinuation was decreased by 18.4 hours with midodrine use ($P = 0.045$). Because of the lack of previously defined subgroup analyses, however, this was a purely hypothesis-generating finding.

A significant limitation of the MIDAS study was the fixed dosing regimen used. It is unknown whether patient-specific dose titration would have resulted in different observations. The inability to uptitrate the dose of midodrine could be a safety precaution as the need for midodrine uptitration could be a marker of clinical deterioration. Additionally, the broad eligibility criteria may have led to a heterogeneous cohort, and the baseline severity of illness, as indicated by APACHE II and Sequential Organ Failure Assessment (SOFA) scores, was relatively low. Despite the long-anticipated results of this randomized controlled trial, more studies are needed to determine the benefits of midodrine for various shock syndromes.

Clinical application and practical considerations

Limitations of published literature. Midodrine is a promising adjunctive agent to facilitate weaning from vasopressors in the recovery phase of vasodilatory shock; however, research related to its use in this setting is limited. The available observational studies had many limitations, including small sample sizes, limited external validity, and a lack of clinically relevant endpoints. Many of these studies failed to report relevant patient information such as comorbidities; fluid resuscitation strategies and fluid status; details of vasopressor selection, dosing strategies, and order of initiation and discontinuation; goal MAP; and use of corticosteroids. Furthermore, midodrine was generally initiated, titrated, and discontinued at the discretion of the clinical team in the absence of a protocol, and the circumstances in which clinicians chose to use this therapy in practice were variable and not well defined. The MIDAS trial had findings contradictory to previous observational studies but was limited by a small sample size, use of a fixed midodrine dose, a heterogeneous patient population, and lack of a priori designation of patient subgroups to be analyzed, despite being a multicenter, double-blinded, randomized controlled trial.

Initiation of drug therapy. The retrospective nature of many of the published studies compounded by the negative findings of the MIDAS trial and the plethora of study limitations has left many clinicians unsure of when it is appropriate to initiate midodrine for patients with vasodilatory shock. Our recommendation is to consider initiating midodrine when the acute phase of vasodilatory shock has resolved and the patient is clinically stable (Figure 1). Resolution of acute shock can be defined as achievement of goal blood pressure while receiving no more than one IV vasopressor with stable or decreasing infusion rates for at least 24 hours.[19,26] Because of risks of bowel ischemia and lack of oral absorption associated with higher doses of vasopressors, we recommend that patients receive no more than 8 μg/min (or 0.1 μg/kg/min) of norepinephrine or its phenylephrine equivalent (Table 2) when initiating midodrine.[21] Clinicians should avoid initiating midodrine in patients receiving epinephrine or dopamine without first exploring the rationale for vasopressor choice. Epinephrine can be used for low cardiac output or bradycardia, while dopamine can be used for bradycardia. Neither of these situations would be suitable for initiation of midodrine because of its depressive effects on cardiac output and heart rate. This threshold for initiating midodrine aligns with the study protocol developed and reviewed by the Food and Drug Administration for MIDAS and is more conservative than the reported baseline vasopressor rates in many of the observational studies of midodrine.[26] Clinically stable patients have no evidence of ongoing end-organ dysfunction, which should include normalization of serum lactate levels, absence of acute troponin elevation, and stable serum creatinine levels.[17] Before prescribing midodrine, clinicians should ensure that all other causes of hypotension, such as hypovolemia and adrenal insufficiency, have been ruled out or appropriately managed.[28]

After other potential causes for persistent vasopressor requirements have been addressed, we recommend initiating midodrine 20 mg orally every 8 hours. This recommendation is

derived from multiple studies that have shown this to be the most common dose required to successfully wean patients from IV vasopressors with no additional adverse effects,[13,19] and, despite the negative findings of the MIDAS trial, we believe this to be a reasonable strategy until more evidence becomes available. When midodrine is used for orthostatic hypotension, it is recommended to reduce the initial midodrine dose for renal dysfunction. However, published studies on the use of adjunctive midodrine in vasodilatory shock did not provide details regarding baseline renal function in study patients, and these studies did not reduce the initial midodrine dose. Therefore, we recommend initiating therapy with midodrine 20 mg orally every 8 hours, regardless of baseline renal function.[19,20] If a patient was on midodrine before ICU admission, it is important to consider underlying pathology and, if treatment is deemed appropriate, to restart the medication to recalibrate to the patient's known baseline. Also, if a patient was on midodrine at home, clinicans could consider reevaluating hemodynamic goals (ie, a MAP goal of >60 mm Hg instead of 65 mm Hg). If home midodrine is resumed and the patient still seems an appropriate candidate for oral vasopressor therapy, consider following the proposed algorithm here but with the dosage additive to the baseline dose. The maximum dose of 40 mg should still be followed.

After administration of midodrine, IV vasopressor dose requirements should decrease within 4 hours of a single dose. On the basis of the pharmacodynamic and pharmacokinetic profile detailed above, the patient would likely have received the maximal benefit within this timeframe. In patients with a lack of initial response, midodrine doses should be uptitrated in 5- to 10-mg increments to a maximum of 40 mg orally every 8 hours. Hammond et al[25] and Whitson et al[19] recommend uptitration in 10-mg increments. We believe that titration by 10 mg, rather than lower doses, will maximize the potential benefits of midodrine in facilitating weaning from IV vasopressors; however, titration in 5-mg increments could also be considered.

Duration of drug therapy. Much of the previously reviewed literature did not describe strategies used for discontinuing midodrine. Careful attention to therapy discontinuation is important, however, to avoid rebound hypotension and ICU readmission. This may also help mitigate polypharmacy resulting from inappropriate

Figure 1. Proposed algorithm for use of midodrine in select patients for liberation from intravenous vasopressors.[19,25] IV indicates intravenous; MAP, mean arterial pressure; SCr, serum creatine; SBP, systolic blood pressure.

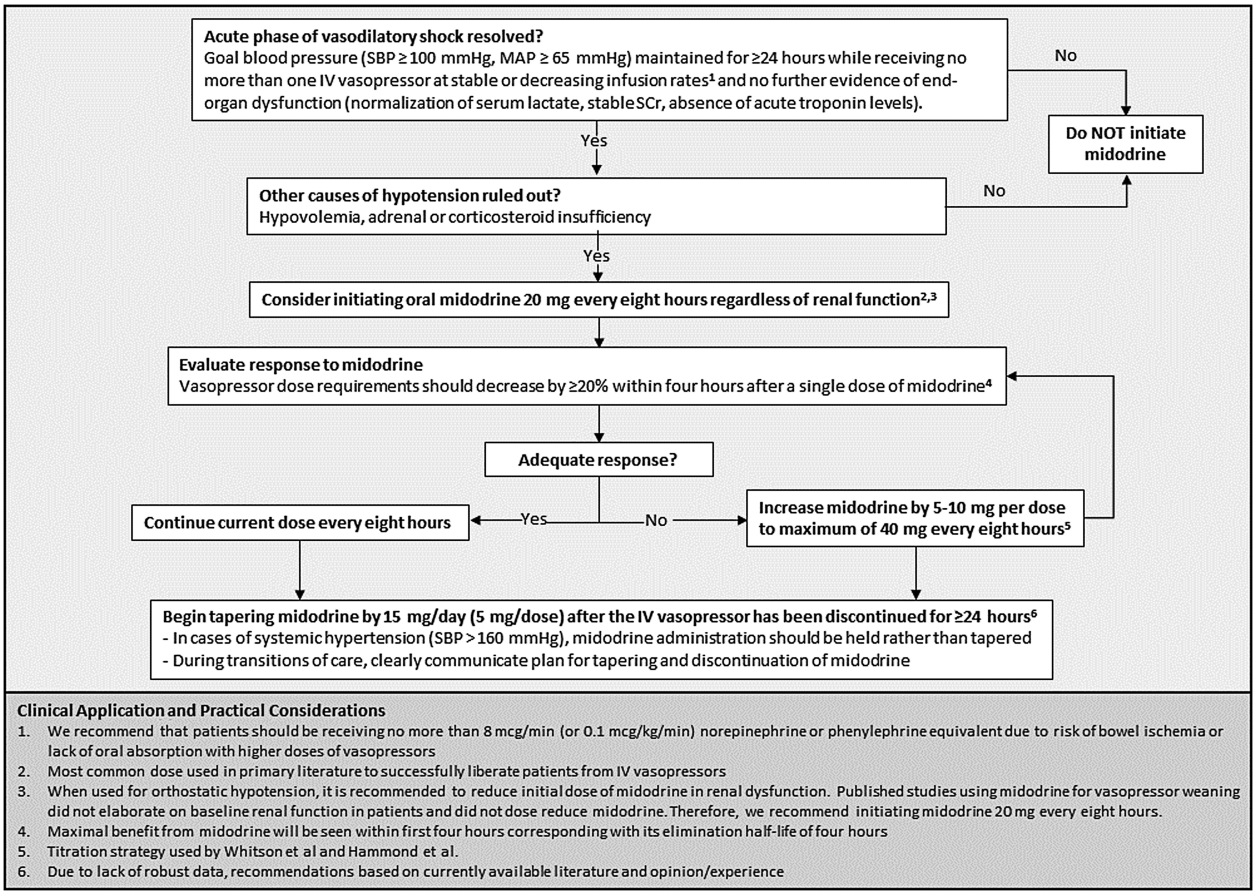

Table 2. Dose Comparison for Commonly Used Intravenous Vasopressors[6,27]

Vasopressor Agent	Equivalent Dose
Norepinephrine	1 μg
Epinephrine	1 μg
Dopamine	100 μg
Vasopressin	0.002 units
Phenylephrine	2.2 μg

continuation of ICU medications and the associated adverse effects.[29] When a patient shows response to midodrine therapy and IV vasopressor doses are decreasing, the clinician should continue to monitor the patient and create a plan for midodrine discontinuation. To ensure that rebound hypotension does not occur, we do not recommend downtitration of midodrine for the first 24 hours following discontinuation of IV vasopressors.[25] Afterward, we recommend decreasing midodrine by 15 mg each day (5 mg per dose) until therapy is stopped.[25] In cases of systemic hypertension, defined by a systolic blood pressure of greater than 160 mm Hg, midodrine administration should be held rather than downtitrated to prevent persistent hypertension. Appropriate management of midodrine therapy during transitions of care as patients transfer from the ICU is important to prevent inappropriate continuation of treatment, which has been seen with other ICU therapies such as stress ulcer prophylaxis and delirium pharmacotherapy.[30,31] Strategies to help wean patients from midodrine after ICU discharge include a detailed plan written in the electronic health record, discussion with the clinical team assuming care of the patient, or creation of a linked titration order with titration instructions (similar to methylprednisolone dose packs) and parameters within the order to hold the medication for hypertension. An emphasis should be placed on creating patient-specific titration schedules in patients with labile blood pressure.

More confounding than its place in the treatment of shock is how or whether midodrine can be used in a transition of care setting. Midodrine may be an effective strategy in facilitating earlier ICU discharge in patients difficult to wean from their remaining vasopressor. Midodrine continuation at the time of ICU discharge was associated with reduced ICU LOS (7.5 vs 10.6 days, $P < 0.001$) and hospital mortality (hazard ratio [HR] = 0.47, $P < 0.001$); however, midodrine continuation at the time of hospital discharge was associated with an increased risk of 1-year mortality (HR = 1.60, $P < 0.001$).[32] Additional factors, such as the utilization of hypertensive therapy, a history of congestive heart failure, and previous cardiac surgery, may be at play when considering the use of outpatient midodrine therapy. In the observational study reported by Whitson et al,[19] 18 of 135 patients (13%) receiving midodrine as an adjunct for vasopressor weaning were discharged from the hospital on this therapy, highlighting the need for careful consideration of midodrine use during each transition of care.

Other adjunctive agents. Other oral agents with α-adrenergic properties such as phenylephrine and pseudoephedrine have been proposed as alternatives to midodrine for liberation from IV vasopressor therapy. While these agents are mechanistically plausible, the lack of both scientific data and clinical experience causes hesitancy about their integration into practice. A review of these alternative agents is outside the scope of this paper.

Conclusion

Midodrine may be an effective oral adjunct to aid in liberating patients from IV vasopressors in the recovery phase of vasodilatory shock. It is important to consider reversible causes of persistent vasodilation, such as hypovolemia and adrenal insufficiency, before initiating midodrine. Monitoring of safety and efficacy is also important, as dose titration is warranted. Intentional communication is imperative during transitions of care to ensure appropriate management of midodrine therapy.

Disclosures

The authors have declared no potential conflicts of interest.

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