THE ROLE OF MIDODRINE FOR HYPOTENSION OUTSIDE OF THE INTENSIVE CARE UNIT
By Lawrence B. Gutman, MD and Ben J Wilson, MD
Lawrence B. Gutman and Ben J. Wilson are with the University of Calgary, Cumming School of Medicine, Calgary, Canada.

Correspondence may be directed to LawrenceBGutman@gmail.com


Abstract
Midodrine is an oral, peripherally acting alpha-adrenergic agonist. After gaining Food and Drug Administration (FDA) approval in 1996 for orthostatic hypotension, its use has evolved to target vasoplegic conditions such as intradialytic hypotension in the end-stage renal disease population, refractory ascites in cirrhotic patients to support diuresis, and in hepatorenal syndrome. Upon oral ingestion, the drug undergoes enzymatic hydrolysis to an active metabolite, desglymidodrine. Its use has been well tolerated at 2.5 mg, 5 mg, and 10 mg oral doses. The most frequently occurring side effects relate directly to its sympathomimetic profile and include piloerection, scalp pruritis, generalized paresthesias, and urinary retention.

The vasoplegic profile of sepsis would be a potential target for midodrine therapy. While its use to mediate recovery from septic shock has been suggested, there is a paucity of clinical data supporting its use. Such therapy may be uniquely appropriate in septic patients who are not candidates for intensive care unit (ICU) level of care.

Key Words: midodrine, vasoplegia, hypotension, sepsis.
Midodrine is an oral, peripherally acting alpha-1 adrenergic receptor agonist. Initially, it gained approval from the FDA in 1996 for orthostatic hypotension on the basis of its ability to increase 1-minute standing blood pressure. Subsequently, its efficacy has been demonstrated in the end-stage renal disease (ESRD) population with intradialytic hypotension, in cirrhotic patients with refractory ascites as a means of supporting diuresis, and in hepatorenal syndrome. There are also reports of its use in post-space flight autonomic insufficiency, tricyclic antidepressant-induced orthostatic hypotension, postprandial hypotension, ejaculatory incompetence, and female urinary incontinence.

However, there is a paucity of data for its use in hypotensive septic patients on the hospital ward or in the emergency department or those deemed inappropriate candidates for intensive care unit (ICU) level care. This may be of critical value in an era where delays in vasopressor initiation in hypotensive septic patients have been shown to increase mortality and organ failure. Midodrine may be a uniquely suited therapeutic adjunct in hypotensive patients—either as a bridge to ICU and intravenous vasopressors or in patients whose goals of care preclude treatment in an ICU. This narrative review will summarize the literature on midodrine in hypotensive, vasoplegic conditions and discuss its potential for use in septic non-ICU patients.

**PHARMACOLOGICAL PROFILE**

Midodrine is a prodrug with 93% bioavailability. Upon oral ingestion, it undergoes enzymatic hydrolysis to an active metabolite, desglymidodrine which acts peripherally as an alpha-1 receptor agonist. Typically, midodrine is administered at 2.5, 5, and 10 mg oral doses and results in dose-dependent increases in systolic blood pressure 1-hour post ingestion with a duration of action of approximately 4 hours after the 10 mg dose. Both venoconstriction and arteriolar vasoconstriction, which augment preload and increase peripheral vascular resistance, mediate the hypertensive effect. Owing to a lack of beta-1 adrenergic properties, midodrine does not cause tachycardia. Rather, as a consequence of its hypertensive effects, there are reports of reflex, parasympathetically-mediated bradycardia with reductions in heart rate by up to 20%. As expected, the use of midodrine with other medications with alpha-1 adrenergic stimulatory properties, such as phenylephrine, ephedrine, and pseudoephedrine may exacerbate hypertension.

In healthy volunteers, oral doses of 2.5 mg demonstrated peak plasma midodrine and desglymidodrine concentrations within 30 and 60 minutes, respectively. Both midodrine and desglymidodrine are renally excreted and neither crosses the blood-brain barrier. The safety profile of midodrine has been well-described. Reported side effects are most commonly the result of direct sympathomimetic activity. In a cohort of 171 patients with orthostatic hypotension, a dose of 10 mg 3 times daily resulted in piloerection (13%), scalp or general pruritis (10% and 2%), scalp or general paraesthesia (9%), urinary retention (6%) and chills (5%). These side effects have been reported with similar frequency in other midodrine trials. There have also been 2 reported cases of dysgeusia and dysosmia following initiation of midodrine at a dose of 5 mg 3 times daily for orthostatic hypotension. Supine hypertension (>180/110 mmHg) is reported in 25% of patients at a dose of 10 mg 3-times daily; however, this risk is minimized when the drug is administered at least 4 hours prior to bedtime. If required, supine hypertension may be reversed with phentolamine, an alpha-1 specific antagonist.

**THERAPEUTIC USES**

**Orthostatic Hypotension**

Orthostatic hypotension (OH), a fall in systolic blood pressure by at least 20 mmHg or diastolic by 10 mmHg upon standing, is prevalent in the elderly, patients with diabetes and in those with Parkinson’s disease. Symptoms of OH include lightheadedness, dizziness and syncope.

The 2 largest, randomized, double-blinded placebo-controlled trials analyzing the safety and efficacy of midodrine in the treatment of OH had a combined total of 268 patients. At a dose of 10 mg 3-times daily for 3 or 4 weeks, patients experienced significant increases in standing systolic blood pressure, with increases up to 22 mm Hg ($p < 0.001$). These results were associated with an improvement in clinical symptoms including depression, dizziness and syncope.
Midodrine has also demonstrated efficacy in diabetic-related orthostasis. A dosing regimen of 10 mg 3 times daily resulted in improved one minute standing systolic blood pressure (118 vs. 96 mmHg 1 hour after receiving the third dose ($p<0.02$)), as well as enhanced cerebral blood flow and cognitive function.6

In both diabetic and non-diabetic-related orthostasis, patients receiving midodrine had improved global evaluation scores, which incorporated lightheadedness, standing time and orthostatic energy levels.6

The efficacy of midodrine in patients with neurogenic orthostatic hypotension (NOH) has also been demonstrated. In the largest study to date, which included 162 patients with NOH of varying etiology, those randomized to midodrine at a dose of 10 mg 3-times daily had significantly higher mean standing systolic blood pressure compared to placebo at 15 days (22 vs 3 mm Hg [$p < 0.001$]). Those receiving midodrine also had significant improvements in lightheadedness ($p = 0.02$).17

In contrast, a recent systematic review and meta-analysis, including 7 trials and 325 patients, concluded that there was insufficient evidence to recommend the use of midodrine as treatment for OH. The authors report statistically insignificant changes in systolic blood pressure and mean arterial pressure between supine and standing positions (4.9 and – 1.7 mmHg, respectively). However, there were statistically significant increases in standing systolic blood pressure (21.5 mmHg, $p <0.001$) and in global symptom assessment. There was significant heterogeneity of included studies, with widely varied patient populations and indications for midodrine. As expected, patients receiving midodrine encountered more adverse effects associated with the drug such as pilomotor reactions and urinary retention.18

**Cirrhosis with Ascites**

The development of ascites in patients with cirrhosis is mediated by elevated portal hydrostatic pressures and splanchnic arterial vasodilation.3 Splanchnic vasodilation may result in renal hypoperfusion; subsequent salt-retaining mechanisms increase total body water and worsen ascites. Current therapeutic approaches to refractory ascites include serial paracentesis, transjugular intrahepatic portosystemic shunt (TIPS) procedures, peritoneovenous shunts and liver transplant.19 Ascites becomes refractory in 5–10% of patients and incurs a 50% 6-month mortality.19

In patients with cirrhosis and ascites, midodrine has been used to increase effective arterial blood volume, through splanchnic vasoconstriction, and enhance renal perfusion and glomerular filtration.20 One study randomized 40 patients with cirrhosis, refractory or recurrent ascites and stable renal function (creatinine <133 μmol/L for >7 days) to standard medical therapy (low sodium diet (<2g daily), furosemide 20–160 mg daily and spironolactone 100–400 mg daily) with or without the addition of midodrine 7.5 mg 3-times daily. Patients receiving midodrine had significantly improved outcomes at 6 months compared to standard medical therapy alone. They had lower body weights, greater urine output and urine sodium excretion, and lower levels of plasma renin and aldosterone activity. MELD scores between the 2 groups were similar at baseline ($p = 0.14$). At 1, 3, and 6-month intervals, MELD scores for patients on standard medical therapy increased significantly (at 6 months, MELD = 19.5 ± 5.1, $p <0.001$) but did not change significantly from baseline in the midodrine group. Overall, median survival was increased in the midodrine arm (365 days vs. 90 days, $p =<0.046$) without compromising renal or hepatic function.19

Although midodrine can mitigate some of the adverse vasodilatory effects of cirrhosis and improve outcomes, it is inferior to albumin for hemodynamic support following large volume paracenteses. A recent systematic review and meta-analyses21 including 3 studies and 114 patients, compared mortality between midodrine and albumin following large volume paracenteses. The use of midodrine alone was associated with increased mortality compared to albumin (OR 10.76, 95% CI 1.35–85.97, $p = 0.03$). As expected, a poorly filled vascular compartment, such as seen after large volume paracentesis, is more amenable to albumin (an intravascular volume expander) therapy compared to the peripherally mediated vasoconstrictive effects of midodrine.

The use of midodrine in hepatorenal syndrome (HRS) has also been described in the literature. A known complication of advanced cirrhosis, HRS manifests...
as renal failure in the setting of splanchnic arteriolar vasodilation, with resultant renal hypoperfusion. Historically, the prognosis associated with untreated HRS has been poor, with median survival of 2 weeks in type I HRS as a result of rapidly progressive renal failure. In a retrospective cohort of 81 patients with similar MELD scores and Child-Pugh classes, 60 patients who received midodrine and octreotide therapy for type I HRS had a significantly lower mortality at 30 days (43%) compared to the remaining 21 patients not on therapy (71%; p < 0.05). Midodrine has resulted in similar positive outcomes in other cohorts with hepatorenal syndrome.

Dialysis-Induced Hypotension

An estimated 20–50% of patients with ESRD encounter symptomatic intradialytic hypotension (IDH). Its cause appears to be multifactorial, relating to intrinsic autonomic dysregulation and rapid fluid removal during ultrafiltration. A number of therapies such as food restriction during dialysis therapy, rescheduling of antihypertensive medications and increasing the dialysate sodium bicarbonate have been trialed with limited success.

Midodrine has also been studied in those with IDH. Small studies have examined the impact of 2.5–10 mg of oral midodrine 15–30 minutes prior to dialysis. Systolic and diastolic blood pressures increased by 11–18 mmHg and 5–6 mmHg, respectively, in patients receiving midodrine therapy. Additionally, patients reported improvements in dizziness, blurred vision, fatigue, nausea and vomiting.

Recovery from Septic Shock

With the high costs associated with intensive care, attempts to safely wean vasopressors have become a priority. The need for continuous intravenous (IV) vasopressor therapy can be a barrier to ICU discharge in select patients. A recent retrospective study investigated the utility of oral midodrine to facilitate IV vasopressor weaning in 275 vasopressor-dependent ICU patients with septic shock. Of these patients, 140 received IV vasopressor only, while the remaining 135 received IV vasopressor and midodrine at an oral dose of 20 mg every 8 hours. The mean duration of IV vasopressor use was 2.9 days in the IV vasopressor with midodrine group compared to 3.8 days in patients receiving IV vasopressors alone (p < 0.001). Length of ICU stay was also shorter in patients receiving IV vasopressor therapy with midodrine (7.5 days compared to 9.4 days in the IV vasopressor only group). Notably, there were no reported complications in patients receiving midodrine, with the exception of transient bradycardia in one patient which resolved upon its discontinuation.

This data is supported by a retrospective analysis of 188 medical ICU patients. In this study, midodrine dosed 2.5–10 mg 2–6-times daily resulted in successful weaning of vasopressors within a median of 1.2 days and was associated with shorter ICU lengths of stay (0.8 vs. 1.5 days, p = 0.01).

Currently, the Midodrine as Adjunctive Support for Treatment of Refractory Hypotension in the Intensive Care Unit: (the MIDAS trial), a multicenter, randomized, placebo-controlled trial is underway to better understand the role of midodrine in expediting IV vasopressor weaning. One hundred twenty medical ICU patients who require low-dose vasopressor but who are otherwise stable for ICU discharge will be randomized to midodrine 20 mg or placebo 3-times daily in addition to usual care. The primary outcome is time from drug administration to discontinuation of IV vasopressor. ICU and hospital length of stay are secondary outcomes.

In a pilot study by the same authors, 20 surgical ICU patients meeting discharge criteria with the exception of low-dose, vasopressor-dependent hypotension (phenylephrine <150 mcg/min or noradrenaline <8 mcg/min) received midodrine (modal dose of 20 mg) 3-times daily. Midodrine facilitated weaning of IV vasopressor in this small population, significantly increasing the rate of IV vasopressor weaning (0.62 mcg/min/hr to 2.20 mcg/min/hr, p = 0.012). In addition, the relatively high midodrine dose used in the study will further inform the side effect profile and tolerability of the drug.

In the non-ICU setting, case reports describe the use of midodrine in expediting vasopressor weaning in the postoperative setting. Midodrine facilitated IV vasopressor weaning following carotid artery stenting and cervical vertebral laminectomy.

Ultimately, trials investigating the use of midodrine for hypotensive patients outside of the ICU would be...
of merit. The use of midodrine in the early phases of sepsis, in emergency department and ward patients prior to ICU admission, is particularly interesting. Such ‘upstream’ use of midodrine may impact vasodilatory physiology at a particularly modifiable phase in the septic inflammatory cascade. Early oral vasopressor use may also limit large volume fluid resuscitation, a practice that has been associated with deleterious outcomes such as worsening organ failure, longer ICU lengths of stay and increased mortality in critically ill patients.34

Ongoing interest in the potential use of midodrine in early sepsis has prompted a prospective, randomized, double blind, placebo-controlled study set to investigate the rate of ICU admissions and intravenous vasopressor use in septic patients.35 The trial will include patients admitted to the ICU within 24 hours of a sepsis diagnosis. Patients will be randomized to receive 3 10 mg doses of oral midodrine or placebo in addition to usual care for sepsis. The trial will also report hemodynamic measures including cumulative vasopressor doses, cardiovascular SOFA scores and mean arterial blood pressures.

In areas of the world without easy access to IV vasopressors, midodrine has been proposed as a useful tool in the management of septic patients.36 Further, its use may prevent potential complications associated with IV vasopressor therapy, such as catheter-related bloodstream infections and risks associated with central line insertion.

CONCLUSION

Midodrine is commonly used to treat several vasoplegic conditions. Its safety and efficacy have been demonstrated in OH, cirrhosis associated with refractory ascites and renal failure, and in intradialytic hypotension. The vasodilatory physiology of sepsis is similar to that characterizing these conditions. It follows that the use of midodrine in this setting would be expected to increase vasoconstriction, improve perfusion, and improve patient outcomes. Indeed, there is emerging data for its utility in ICU patients with septic shock.

Midodrine may be a useful adjunct for select non-ICU patients with sepsis. It may be a reasonable vasopressor for septic patients in developing countries lacking access to IV vasopressors, as a bridge to ICU to optimize early vasopressor use, or in the ward population who are inappropriate for the ICU. Other potential patients who may benefit are those with difficult IV access or not wanting invasive central lines. There is a role for its use in stable ICU patients ready for discharge with the exception of mild, vasopressor-dependent hypotension. Patients being transferred to the ICU from the ward, or those en route to hospital with a tenuous hemodynamic state may also benefit from temporization with midodrine. Clinical trials investigating the use of midodrine in these settings are clearly warranted.

REFERENCES

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