Midodrine use in critically ill patients: a narrative review

Rahul Costa-Pinto, Daryl A Jones, Andrew A Udy, Stephen J Warrillow and Rinaldo Bellomo

Midodrine is an oral vasopressor agent that is receiving increasing interest as a therapy to reduce intensive care unit (ICU) admission and length of stay for patients who would otherwise require intravenous vasopressor infusions and invasive monitoring. Although usage trends increase, evidence for its effectiveness is conflicting. Adequacy and frequency of dosage, timing of initiation and patient selection are important factors to consider when prescribing midodrine for critically ill patients. This narrative review explores the historical context of midodrine usage, its pharmacological properties, current trends in use both within and outside the critical care environment, evidence to support its use, and finally, future research directions.

Historical context

Midodrine was patented in 1965 by Chemie Linz AG[1] in Linz, Austria, and was first described in the medical literature in the 1970s as a novel peripherally acting α-agonist with good enteral absorption, efficacy and a long duration of action.[2] Animal experiments revealed that α-(2,5-dimethoxyphenyl)-β-glycinamido-ethanol hydrochloride, or midodrine, and its active metabolite α-(2,5-dimethoxyphenyl)-β-aminoethanol (ST-1059 or desglymidodrine) effectively increase peripheral vascular tone and stimulate α-adrenergic receptors in intestine, bladder, bronchi and pupils[2] without directly affecting cerebral blood flow.[3]

Plasma levels of the active metabolite, desglymidodrine, were significantly correlated with pressor activity,[4] and midodrine's reported venoconstrictive effect was 50–80% of noradrenaline-induced venoconstriction in vitro.[5,6] Unlike other sympathomimetic agents with pressor effects, midodrine was equally efficacious in parenteral and enteral formulations.[2]

Subsequent observational studies found clinical utility for midodrine's α-sympathomimetic action and ease of oral administration for conditions such as urinary stress incontinence[7,8] and ejaculation disorders,[9,10] as well as orthostatic hypotension related to neurological conditions,[11] neuroleptic medications[12] and idiopathic postural hypotension in paediatric and adult populations.[13-15]

ABSTRACT

Midodrine is a peripherally acting, oral α-agonist that is increasingly used in intensive care units despite conflicting evidence for its effectiveness. It has pharmacological effects on blood vessels as well as pupillary, cardiac, renal, gastrointestinal, genitourinary, lymphatic and skin tissue. It has approval for use as a treatment for orthostatic hypotension, but a surge in interest over the past decade has prompted its use for a growing number of off-label indications. In critically ill patients, midodrine has been used as either an adjunctive oral therapy to wean vasoplegic patients off low dose intravenous vasopressor infusions, or as an oral vasopressor agent to prevent or minimise the need for intravenous infusion. Clinical trials have mostly focused on midodrine as an intravenous vasopressor weaning agent. Early retrospective studies supported its use for this indication, but more recent randomised controlled trials have largely refuted this practice. Key questions remain on its role in managing critically ill patients before intensive care admission, during intensive care stay, and following discharge. This narrative review presents a comprehensive overview of midodrine use for the critical care physician and highlights why lingering questions around ideal patient selection, dosing, timing of initiation, and efficacy of midodrine for critically ill patients remain unanswered.

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These pilot studies typically used oral doses of 2.5–5 mg two or three times daily. An early observational study also demonstrated midodrine's safety and efficacy in increasing blood pressure in children with septic shock.[16] Most of these early, small observational and double-blind studies reported minimal adverse events.

Larger clinical trials in the 1990s established midodrine as a safe and effective agent for orthostatic hypotension.[17-20] The first multicentre, double-blind, randomised controlled trial (RCT) evaluating the use of midodrine for moderate to

severe orthostatic hypotension was conducted in the United States and published in 1993.[17] This study assigned its 97 patients to either receive placebo, or midodrine at doses of 2.5 mg, 5 mg or 10 mg over a 4-week period. At 10 mg doses, midodrine increased standing systolic blood pressure by 28% and, at all doses, significantly improved symptoms of dizziness, weakness and syncope. A larger double-blind study of 171 patients, administering midodrine at 10 mg three times daily for a 4-week period found a similar increase in standing systolic blood pressure (24% mean increase) and reduction in mean symptom score for lightheadedness.[19] These studies paved the way for midodrine to receive United States Food and Drug Administration (FDA) approval in 1996 for symptomatic orthostatic hypotension via its Accelerated Approval Program.

Other emerging uses for midodrine were also reported around this time. Midodrine as a pre-medication for chronic hypotension associated with haemodialysis was shown to be safe and provided extended haemodynamic and symptomatic benefit in doses ranging from 2.5 mg to 25 mg.[21-24] Midodrine for reversal of hepatorenal syndrome was also described[25,26] to improve renal plasma flow and glomerular filtration rate with improved one-month survival.

In 2010, however, the FDA decided to withdraw midodrine from the market due to the failure of its manufacturers to conduct any post-marketing studies to confirm clinical benefit for orthostatic hypotension.[27] Health care professional appeals and consumer complaints led to this action being delayed[28,29] pending phase 4 trials. A phase 4, double-blind, placebo-controlled, randomised tilt-table study was finally published in 2016 which showed that patients receiving stable doses of midodrine for more than 3 months had a statistically significant increase in time to tilt-table-induced syncopal symptoms.[30] Nevertheless, this scrutiny stimulated interest to demonstrate midodrine's efficacy across many patient groups and clinical settings, with more than half of all published literature on midodrine appearing since this time.

Pharmacology of midodrine

Midodrine is a peripherally acting α-receptor agonist available as 2.5 mg and 5 mg tablets. It does not act preferentially on either α_1- or α_2-receptors,[31] but its active metabolite, desglymidodrine, selectively stimulates α_1-receptors.[32] It causes modest increases in supine and standing blood pressure in a dose-dependent manner.[2,20] Its other pharmacodynamic effects are to increase peripheral vascular resistance, increase venous tone and release of atrial natriuretic peptide,[33] and reduce circulating plasma and blood volume[31] (Figure 1).

Midodrine has poor blood-brain barrier penetration[34] and, therefore, no direct central nervous system activity. It has no myocardial β-adrenoreceptor activity but indirectly increases end-diastolic volume and stroke volume, decreases heart rate and circulating noradrenaline levels via baroreceptor stimulation,[35,36] and causes QT prolongation.[37] It has no significant metabolic or endocrine effects. It has no effect on serum lipids, insulin, or uric acid levels.[38] It also does not have any established effect on pulmonary, renal,[34] coagulation[39] or immune function.[40] It has been safely administered in pregnancy.[41,42]

Desglymidodrine, the active metabolite, is generated from midodrine by the enzymatic cleavage of the amino acid glycine. The oral bioavailability of desglymidodrine is 93%. The mean maximum concentration in plasma for midodrine is 20–30 minutes after oral administration and 60 minutes for desglymidodrine.[43] Binding to plasma proteins is less than 30%. Midodrine is cleared from plasma after 2 hours,[31] with an elimination half-life of 30 minutes.[43] The elimination half-life of desglymidodrine is 3 hours.[43]

Midodrine undergoes extensive metabolism in various tissues including the liver (predominantly by cytochrome P450 isoforms CYP2D6 and CYP1A2[44]), with only 4% of a single dose excreted unchanged.[31] Excretion of midodrine and desglymidodrine is primarily urinary. Haemodialysis can reduce the elimination half-life of desglymidodrine to 90 minutes. In end-stage chronic kidney disease, the elimination half-life can be as long as 10 hours.[45]

Common adverse effects are related to midodrine's α-agonist properties. Pilomotor reactions (piloerection, scalp pruritus) are the most frequently reported adverse effects followed by gastrointestinal and genitourinary complaints (nausea, abdominal pain, urinary retention, dysuria), cardiovascular effects (supine hypertension, bradycardia) and central nervous system effects (paraesthesia, taste and smell disturbance). Although up to 80% of patients may experience one or more of these adverse effects,[46] they are dose-dependent and generally mild. Singular case reports describe midodrine use associated with takotsubo cardiomyopathy,[47] intracerebral haemorrhage,[48] reversible cerebral vasoconstriction syndrome,[49] myoclonic seizures,[50] vascular ischaemia,[51] and ileus.[52]

In critical care settings, when administered as an intravenous vasopressor weaning agent, the most common adverse effect is reflex bradycardia[53] which is proportional to midodrine dose.[54] Drug interactions may occur with concomitant prescription of antiarrhythmics, β-blockers, antipsychotics, monoamine oxidase inhibitors and tricyclic antidepressants metabolised by cytochrome CYP2D6[55] as well as ranitidine, metformin and procainamide, which compete with desglymidodrine at acute tubular secretion sites in the kidney.[56]

Midodrine daily doses of up to 120 mg (in divided doses) have been reported in the literature with no adverse effects,

Figure 1. Pharmacological effects of midodrine in various organ systems

Pupils

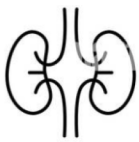
Mydriasis

Heart

↑ End-diastolic volume
↑ Stroke volume
↑ QT interval
↓ Heart rate (reflex bradycardia)
Release of atrial natriuretic peptide

Blood vessels

↑ Peripheral vascular resistance
↓ Circulating noradrenaline levels (via baroreceptor stimulation)
↓ Plasma volume



Kidneys

↑ Renal plasma flow
↑ Glomerular filtration rate

Gut

↑ Lower oesophageal sphincter contraction
↑ Colonic smooth muscle relaxation (ileus)

Bladder and sexual organs

↑ Bladder internal sphincter/detrusor tone
↑ Urethral closing pressure
↑ Vas deferens contraction

Lymph nodes, muscle and skin

↓ Lymphatic flow
Piloerection
Pruritus

even in patients with end-stage chronic kidney disease.[53,57-58] Overdosage may present as severe hypertension, bradycardia, urinary retention and piloerection.[59] Hypertension can be managed with nitrovasodilator or α-sympatholytic infusions (glyceryl trinitrate, sodium nitroprusside, phentolamine). Bradycardia can be managed with atropine.

Midodrine use outside critical care settings

Aside from its well established uses for orthostatic hypotension and neurocardiogenic syncope,[60] midodrine has been used off-label for multiple clinical indications over the past 20 years. Case reports and case series report its use to maintain normotension in patients with a spinal cord injury[61] and following acute myocardial infarction,[62] to correct dysautonomia in chronic fatigue syndrome,[63] to decrease left ventricular outflow tract obstruction by improving filling in hypertrophic cardiomyopathy,[64] to decrease severity of shunt and hypoxemia in patients with right-to-left intracardiac shunting,[65] to increase systemic vascular resistance and reduce pulmonary pressures in porto-pulmonary hypertension,[66] and to decrease lymphatic flow in refractory chylothorax.[67,68]

Small prospective studies have demonstrated its use to maintain perfusion pressure in acute stroke[69] and following carotid endarterectomy,[70] to mitigate treatment-induced hypotension in advanced heart failure,[71] to enhance exercise tolerance and sexual function in patients with a spinal cord injury,[72-74] to reduce severity of symptoms in refractory gastro-oesophageal reflux disease,[75] and to manage orthostatic intolerance with mobilisation following total hip and knee replacement.[76]

Randomised trials weakly support the use of midodrine for stress urinary incontinence in women.[77] There are conflicting RCT data for its efficacy in preventing paracentesis-induced circulatory dysfunction[78-81] and recurrence of ascites as a substitute for albumin in patients with cirrhosis.[82,83]

There is a much larger number of studies and now meta-analyses and systematic reviews that support its use as a treatment for orthostatic hypotension and recurrent vasovagal syncope,[84,85] intradialytic hypotension[86] and hepatorenal syndrome.[87] However, even for these indications, the pooled evidence for

Table 1. All published retrospective, prospective and randomised controlled trials of midodrine as a vasopressor weaning agent in intensive care units (ICUs)*

First author (year)	Design	Setting (sample size)	Midodrine dose (frequency)	IV VP weaned	Results
Retrospective studies					
Whitson[58] (2016)	Observational, controlled	Medical ICU (*n* = 275)	10–40 mg (8-hourly)	Noradrenaline, phenylephrine	• Shorter duration of IV VP (mean, 2.9 *v* 3.8 days; *P* < 0.001) • Shorter ICU LOS (mean, 7.5 *v* 9.4 days; *P* = 0.017)
Poveromo[97] (2016)	Observational, controlled	Mixed ICU (*n* = 188)	2.5–10 mg (4- to 12-hourly)	Adrenaline, dopamine, noradrenaline, phenylephrine, vasopressin	• Lower IV VP dose at 24 hours (median, reduction of 97.3%) • No difference in ICU LOS (median, 5.5 *v* 5.0 days; *P* = 0.29)
Rizvi[53] (2018)	Observational, uncontrolled	Mixed ICU (*n* = 1119)	5–30 mg (8-hourly)	Adrenaline, dopamine, noradrenaline, phenylephrine, vasopressin	• Fewer patients on IV VP at 24 hours (663 *v* 344; *P* < 0.001)
Tremblay[98] (2020)	Observational, propensity matched	Cardiac ICU (*n* = 148)	Mostly 10 mg (8-hourly)	Adrenaline, noradrenaline, vasopressin	• No difference in duration of IV VP (median, 63 *v* 44 hours; *P* = 0.052) • Longer ICU LOS (median, 99 *v* 68 hours; *P* = 0.001)
Macielak[99] (2021)	Observational, uncontrolled	Mixed ICU (*n* = 44)	5–20 mg (6-hourly)	Adrenaline, dopamine, noradrenaline, phenylephrine, vasopressin	• Lower IV VP dose at 24 hours (mean, reduction of 40%)
Prospective studies					
Levine[100] (2013)	Observational, uncontrolled	Surgical ICU (*n* = 20)	5–20 mg (8-hourly)	Noradrenaline, phenylephrine	• Faster decline in IV VP rate after four doses (mean, −0.62 *v* −2.20 µg/min; *P* = 0.012)
Randomised controlled trials					
Santer[101] (2020)	Randomised, placebo controlled	Mixed ICU (*n* = 132)	20 mg (8-hourly)	Metaraminol, noradrenaline, phenylephrine	• No difference in duration of IV VP (median, 23.5 *v* 22.5 hours; *P* = 0.62) • No difference in ICU LOS (median, 6 *v* 6 days; *P* = 0.46)
Lal[102] (2021)	Randomised, placebo controlled	Medical ICU (*n* = 32)	10 mg (8-hourly)	Adrenaline, dopamine, noradrenaline, phenylephrine, vasopressin	• No difference in duration of IV VP (median, 14.5 *v* 18.8 hours; *P* = 0.19) • No difference in ICU LOS (median, 2.29 *v* 2.45 days; *P* = 0.36)
Costa-Pinto[54] (2022)	Randomised, open-label controlled	Mixed ICU (*n* = 62)	10 mg (8-hourly)	Metaraminol, noradrenaline	• No difference in duration of IV VP (median, 16.5 *v* 19.0 hours; *P* = 0.22) • No difference in ICU LOS (median, 50 *v* 59 hours; *P* = 0.14)
Adly[103] (2022)	Randomised, open-label controlled	Medical ICU (*n* = 60)	10 mg (8-hourly)	Noradrenaline	• Shorter duration of IV VP (median, 26.0 *v* 78.5 hours; *P* < 0.001) • No difference in ICU LOS (mean, 11.9 *v* 11.5 days; *P* = 0.876)
Ahmed Ali[104] (2022)	Randomised, open-label controlled	Surgical ICU (*n* = 90)	10 mg (8-hourly)	Noradrenaline	• Shorter duration of IV VP (mean, 3.30 *v* 6.93 days; *P* < 0.001) • Shorter ICU LOS (mean, 5.13 *v* 9.03 days; *P* < 0.001)

IV = intravenous; LOS = length of stay; VP = vasopressor. * Abstracts not included.

midodrine has often been inconsistent and of low quality. Midodrine use for intradialytic hypotension is associated with higher pre-transplant rates of all-cause hospitalisation, cardiovascular hospitalisation, and death[88] as well as poorer post-transplant outcomes.[89,90] It is also less effective in improving renal outcomes and survival in type 1 hepatorenal syndrome than terlipressin or noradrenaline.[91,92]

Rationale and evidence for midodrine in the ICU

The use of midodrine in the ICU was first described in 2002 for a patient following an emergency multilevel laminectomy for acute thoracic spinal cord compression. Postoperatively, it appeared to be an effective noradrenaline substitute, negating the requirement for central venous access and reducing ICU length of stay.[93]

Midodrine use in critically ill patients, thereafter, has mostly been as either an adjunctive oral therapy to wean vasoplegic patients off low dose intravenous vasopressor infusions, or as an oral vasopressor agent to prevent or minimise the need for intravenous infusion.[53] There are several reasons why these remain attractive indications. Firstly, midodrine has a reasonable safety profile and is relatively inexpensive (less than $1.00 per 5 mg tablet). Secondly, effective use of an oral vasopressor may avoid the potential complications of central line insertion and catheter-related bloodstream infections.[94] Thirdly, oral vasopressors may offer an alternative for patients with comorbid conditions not suitable for ICU admission or as a palliative strategy for patients discharged from the ICU.[95] Finally, shortening the duration of intravenous vasopressor support may decrease ICU and hospital length of stay, reducing cost and improving health care access.[96]

Clinical trials have mostly focused on midodrine as an intravenous vasopressor weaning agent (Table 1). Early retrospective studies used modal doses of 10–20 mg 8-hourly for patients requiring intravenous vasopressors for septic shock, trauma and cardiovascular diagnoses and showed that intravenous vasopressor discontinuation occurred a median of 1.2–2.9 days after midodrine initiation or, alternatively, midodrine reduced intravenous vasopressor duration by up to 25%.[58,97,105] The most commonly weaned vasopressor infusions were phenylephrine and noradrenaline, but patients were also weaned off adrenaline, dopamine and vasopressin. These non-randomised trials showed midodrine could be safely administered in critically ill patients in doses ranging from 10 mg 8-hourly to 40 mg 8-hourly.

In contrast, the largest retrospective study of midodrine use as a vasopressor weaning agent included 2070 patients (209 adjunctive midodrine patients, 1861 intravenous vasopressor-only patients) with predominantly septic shock and found a longer intravenous vasopressor duration in the midodrine group and no difference in ICU or hospital length of stay.[106] This study enrolled patients who required intravenous vasopressor for more than 7 days, so it is likely they received midodrine later in their ICU stay or had more persistent refractory vasoplegia. In combination, findings from these retrospective studies did not support the use of midodrine as a weaning agent.[107]

Another retrospective study of 74 cardiothoracic surgery patients who received midodrine to wean intravenous vasopressor support also found no difference in length of vasopressor duration compared with a propensity score matched control group. Of concern, however, midodrine use was associated with longer ICU length of stay and higher mortality in this study.[98]

The first prospective study examining this indication for midodrine was an observational study of 20 surgical ICU patients who received a modal dose of 20 mg (range, 5–20 mg) 8-hourly to wean off phenylephrine or noradrenaline infusions.[100] Midodrine significantly reduced the dose of intravenous vasopressors and 70% of patients were completely weaned after four doses of midodrine. Clearly, given these mixed findings across relatively small retrospective and prospective studies, large RCTs were required to answer this important clinical question.

The first double-blind RCT to investigate the efficacy of midodrine as an intravenous vasopressor weaning agent, the MIDAS study, was registered in 2012 (ClinicalTrials.gov NCT01531959) and published in 2020.[101] This international, multicentre study included all hypotensive (systolic blood pressure < 90 mmHg) patients requiring single agent intravenous vasopressor support for more than 24 hours across three tertiary referral hospitals. Exclusion criteria included high dose vasopressor support (ie, noradrenaline > 8 μg/min, phenylephrine > 100 μg/min, metaraminol > 60 μg/min), patients with ongoing clinical evidence of shock, and chronic kidney, liver and heart disease. Patients were randomised to receive either 20 mg midodrine 8-hourly, or placebo until 24 hours after cessation of intravenous vasopressor.

Overall, 132 patients were randomised in a 1:1 ratio over 7 years. Midodrine use was not associated with any differences in time to intravenous vasopressor cessation (median, 23.5 [interquartile range (IQR), 10.0–54.0] *v* 22.5 [IQR, 10.4–40.0] hours) nor ICU or hospital length of stay when compared with placebo.

The MAVERIC study,[54] a multicentre open-label RCT, used similar inclusion and exclusion criteria but utilised a lower midodrine dose (10 mg 8-hourly) and reported similar findings to the MIDAS study. The median time to discontinuation of intravenous vasopressor was 16.5 hours

(IQR, 7.5–27.5 hours) in the midodrine group and 19 hours (IQR, 12.25–38.5 hours) in the control group ($P = 0.32$). Again, ICU and hospital length of stay were similar between groups.

In contrast to these two negative RCTs, a single centre open-label RCT including 60 patients in Egypt[103] found a striking difference in time to intravenous vasopressor cessation using midodrine 10 mg 8-hourly for patients with septic shock receiving stable low dose intravenous vasopressor for at least 24 hours at the time of randomisation. The median time to intravenous vasopressor cessation was 26 hours (IQR, 14–106 hours) in the midodrine group and 78.5 hours (IQR, 32–280 hours) in the control group. However, in-hospital mortality was very high across both groups in this study (43.3% in the midodrine group and 73.3% in the control group), which makes generalisability of these results, without adjusting for mortality, problematic.

The MIDAS and MAVERIC studies strongly question the utility of midodrine as an intravenous vasopressor weaning agent. One postulated mechanism for this lack of effect is that in patients with chronic hypotension, increased baroreceptor sensitivity (baroreceptor habituation) may limit the utility of midodrine administration. These patients have increased heart rate variability and respiratory sinus arrhythmia compared with healthy control subjects, suggesting both increased parasympathetic cardiac tone and reduced sympathetic activity.[108] In turn, there is no significant increase in cardiac output following midodrine administration in this patient population.[109]

Other postulated mechanisms for midodrine's lack of efficacy as a vasopressor weaning agent include the multifactorial aetiology of hypotension in critically ill patients, downregulation of adrenergic receptors with chronic vasopressor infusions,[110] and unpredictable oral absorption due to gastrointestinal tract oedema or intestinal vasoconstriction.[111] Partial or complete interruption of cardiovascular innervation (such as that seen in tetraplegia)[112] as well as central arterial stiffness[113] will also affect individual responses to midodrine.

Further considerations in the critically ill patient

One limitation of all RCT evidence thus far for midodrine as a vasopressor weaning agent is protocolised fixed drug dosing.[114] Published RCTs have all either utilised 10 mg or 20 mg midodrine at 8-hourly dose intervals. This differs to normal clinical practice where vasopressor support is usually titrated to a mean arterial pressure (MAP) target in real time. An adaptive midodrine dose-titration protocol in an RCT design may help answer this question. However, such a trial would have significant implementation challenges in a critically ill cohort of patients where drug half-life and oral bioavailability may be unpredictable compared with rapidly titratable intravenous therapies.[115]

An alternative approach could involve increased dosing frequency of midodrine given its 3-hour half-life. A retrospective study of 23 patients receiving midodrine at 6-hourly intervals to wean off intravenous vasopressors[99] found this regimen to be safe. Prospective trials are required to test this hypothesis.

Bradycardia appears to be a major limitation for trialling higher doses of midodrine in the ICU. No patients receiving 10 mg midodrine 8-hourly in the MAVERIC study had an episode of severe bradycardia (heart rate < 40 beats per minute). In contrast, 7.6% of patients receiving midodrine 20 mg 8-hourly had an episode of severe bradycardia in the MIDAS study, suggesting a dose-dependent response. Severe bradycardia may prevent ICU discharge regardless of intravenous vasopressor requirements and limit the usefulness of midodrine for this indication.

In both the MIDAS and MAVERIC RCTs, intravenous vasopressors were ceased within 24 hours in the placebo group questioning whether patients who are receiving stable low doses of intravenous vasopressors for more than 24 hours are the group most likely to benefit from adjunctive midodrine. A recently completed multicentre, pilot, feasibility double-blinded RCT of patients with sepsis of less than 24 hours duration[102] suggests a larger clinical trial is warranted to explore earlier initiation of midodrine. In this study, 32 patients were randomised to receive three doses of midodrine 10 mg at 8-hourly intervals or placebo. The intervention occurred at a median time of 13 hours following admission to the ICU. There was no significant difference in duration of intravenous vasopressors or ICU length of stay and no adverse events reported.

RCTs have thus far included a heterogeneous population of critically ill patients. This may be problematic as the underlying mechanisms of hypotension in the ICU are varied and may include sepsis-driven cytokine release, adrenal insufficiency, medication or anaesthesia-related vasoplegia, hypovolaemia or inadequate cardiac output. Interestingly, a *post hoc* subgroup analysis in the MIDAS study found that the 31 patients with epidural analgesia had a significantly shorter duration of intravenous vasopressor therapy when administered midodrine compared with placebo (–18.4-hour difference; 95% CI, –33.5 to –3.3 hours; $P = 0.045$).[101] This homogenous group of postoperative patients with neurogenic vasoplegia may be one such patient cohort to benefit from midodrine and should be studied further. Further evidence of this effect was seen in a recent single centre RCT in an Egyptian trauma ICU,[104] which found the addition of midodrine halved the duration of intravenous vasopressor support in 30 patients with spinal cord injury and neurogenic shock (3.3 ± 1.32 days for adjunctive midodrine; 6.93 ± 2.32 days for intravenous vasopressor alone). However, this was an open label study and a lower

Figure 2. Research priorities for the use of midodrine in critically ill patients

1. Midodrine as an early IV VP alternative?
2. Midodrine as an early IV VP adjunct?

1. Optimal midodrine dose?
2. Optimal midodrine frequency?
3. Optimal timing of midodrine initiation?
4. Optimal patient selection?
5. Feasibility of adaptive midodrine dose-titration studies?

1. Safety and compliance of midodrine weaning protocols?
2. Long term outcomes of post-ICU patients on midodrine?

ICU = intensive care unit; IV = intravenous; VP = vasopressor.

MAP was achieved in the midodrine group, which may have affected the results.

Future directions and research priorities

Even though almost all prospective trials have failed to demonstrate clinical benefit thus far, interest remains in definitively establishing whether oral midodrine can wean ICU patients from intravenous vasopressor support more rapidly (Figure 2). The LIBERATE study[116] is a Canadian multicentre, blinded RCT aiming to recruit 350 patients receiving stable intravenous vasopressor support to assess if midodrine 10 mg 8-hourly can shorten ICU length of stay.

Trials investigating the "upstream" use of midodrine are currently lacking and would be of significant interest. A large retrospective, single-centre study of 1119 hypotensive patients who were administered midodrine in the ICU found that 41% were not receiving an intravenous vasopressor infusion at the time, and of these, 90% avoided the need for intravenous vasopressor after commencing midodrine.[53] Prospective, randomised studies examining the role of midodrine before intravenous vasopressor infusions as either an alternative or adjunctive agent for patients in the emergency department, ward and intensive care settings would be of great value.

Finally, it is important to note that up to two-thirds of ICU patients who commence midodrine are discharged from the ICU on midodrine, and between one-third and half of all patients discharged from hospital remain on the medication.[111,117] Discharge from hospital on midodrine was associated with a 1.6-fold higher risk of one-year mortality.[111] Weaning protocols were utilised in both the MIDAS and MAVERIC studies, and only 6.2% of patients in the MAVERIC study continued midodrine beyond the study period,[54] suggesting such protocols may reduce the ongoing prescription of midodrine outside the ICU. Safety and compliance with midodrine weaning protocols merits further investigation.

Conclusions

This narrative review presents a comprehensive overview of midodrine use for the critical care physician coursing its early utilisation as a novel oral vasopressor for a range of outpatient indications through to its incremental use in ICUs around the world. Research interest has been piqued and will help shed light on the lingering questions around ideal patient selection, dosing, timing of initiation, and efficacy of midodrine for critically ill patients.

Competing interests

All authors declare that they do not have any potential conflict of interest in relation to this manuscript.

Author details

Rahul Costa-Pinto[1,2]
Daryl A Jones[1,2]
Andrew A Udy[3,4]
Stephen J Warrillow[1,2]
Rinaldo Bellomo[1,2,4,5]

1 Department of Intensive Care, Austin Hospital, Melbourne, VIC, Australia.

2 Department of Critical Care, Department of Medicine, University of Melbourne, Melbourne, VIC, Australia.
3 Department of Intensive Care, Alfred Hospital, Melbourne, VIC, Australia.
4 Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia.
5 Data Analytics Research and Evaluation Centre, University of Melbourne and Austin Hospital, Melbourne, VIC, Australia.

***Correspondence*:** rahul.costa-pinto@austin.org.au

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