

Beneficial Effect of Midodrine in Hypotensive Cirrhotic Patients with Refractory Ascites

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Ascites is the most frequent complication of cirrhosis, occurring in nearly 50% of patients within 10 years after cirrhosis is diagnosed.¹ A proportion of these patients require large-volume paracentesis (LVP) for symptom relief when other treatment modalities are unsuccessful or impossible. However, frequent LVP is associated with patient discomfort, decreased quality of life, and increased potential risks, such as circulatory dysfunction and related complications.² Vasoconstrictors are known to have beneficial effects in patients with hepatorenal syndrome (HRS), as these agents can improve renal disease related to circulatory dysfunction.³⁻⁵ We report 2 patients requiring frequent LVP who benefited from midodrine treatment, as evidenced by the decreased volume of ascitic fluid drained; midodrine treatment also reduced the frequency of paracentesis and, thus, its potential risks.

Patient #1

A 47-year-old man with cryptogenic cirrhosis and sudden onset of ascites was seen in May 2008. His Model for End-Stage Liver Disease (MELD) score was 23, and his Child-Pugh score was 8. He required frequent LVP to control his symptoms. His past medical history was significant for congenital heart disease that was surgically corrected at a young age; he had residual mild pulmonary hypertension. The patient had been infected with HIV and was receiving antiretroviral therapy; he had negative RNA titers and a CD4 T-cell count of approximately 600 cells/mm³. He also had a history of diabetes and lipodystrophy related to his HIV infection and its medications. He had been

on hemodialysis since 2005 for HIV-related nephropathy and was not on diuretics. He had no significant past or current alcohol intake, and he tested negative for hepatitis B and C virus infection, autoimmune markers, inherited disorders, and metabolic liver disease.

The patient had required frequent paracentesis for ascites since the onset of this complication in May 2008. A transjugular liver biopsy was consistent with cryptogenic cirrhosis. His right atrial pressure was 11 mmHg, with a hepatic venous wedge pressure gradient of 15 mmHg. As shown in Table 1, the patient had required 9 paracentesis procedures over a 2-month period, resulting in the drainage of 57 L of ascitic fluid.

Midodrine treatment was initiated, and the dose was gradually increased to 5 mg TID for low blood pressure while on dialysis. His blood pressure improved from 73 mmHg systolic to 102 mmHg systolic with this intervention. There was no increase in fluid filtered by dialysis, but the volume of ascitic fluid drained decreased to 11 L during 2 months of midodrine treatment. He required 4 paracentesis procedures during this period. His post-paracentesis weight was stable before and during midodrine therapy.

Patient #2

A 59-year-old woman with a history of alcoholic cirrhosis diagnosed in January 2008 developed HRS requiring hemodialysis in March 2008. She began regular LVP for ascites that same month. She was not receiving diuretic medications while on dialysis. Her MELD and Child-Pugh scores were 24 and 8, respectively. She had hypotension that was treated with midodrine at an initial dose of 2.5 mg TID; this dose was gradually increased to 12.5 mg TID by September 2008. Her blood pressure improved

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Table 1. Effect of Midodrine on Large-Volume Paracentesis

	Prepeak Midodrine			Postpeak Midodrine		
	Systolic BP (mmHg)	Ascites		Systolic BP (mmHg)	Ascites	
		Frequency	Volume (L)		Frequency	Volume (L)
Patient #1	73	9	57	102	4	11
Patient #2	67	6	45	93	4	19

Ascites outcomes were compared for a similar time period pre- and postmidodrine for each patient.

BP=blood pressure.

from approximately 70 mmHg systolic to approximately 90 mmHg systolic.

The amount of fluid filtered by dialysis during this period did not change. However, the amount of ascitic fluid drained to reach the patient's baseline weight decreased from 45 L during the 40-day period prior to her maximum dose of midodrine to 19 L during the 38-day period following the maximum dose of midodrine; her blood pressure also improved, and the volume of fluid drained during LVP decreased. The frequency of ascites drainage also decreased from 6 procedures to 4 procedures during the same time periods.

Discussion

The pathophysiology of ascites is complex, and various mechanisms have been proposed. Splanchnic and systemic vasodilation related to excess nitric oxide has been associated with systemic hypotension and increased portal flow.⁶ This is associated with hemodynamic compensatory mechanisms via activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and the nonosmotic release of antidiuretic hormones.¹

Various vasoconstrictors have been used in the management of HRS, including noradrenaline, terlipressin, octreotide, and midodrine.³⁻⁵ Among these agents, midodrine appears to be effective and offers the convenience of oral administration.⁵ Midodrine has also been shown to be safe and effective for preventing dialysis-induced hypotension and improving systolic blood pressure, but there is no significant increase in the volume of fluid filtered by dialysis, nor is there a change in body weight in these patients.^{7,8} The beneficial effects of midodrine have been attributed to its modulating effects on autonomic function and increased peripheral blood vessel resistance.⁹

Midodrine has also been used for the management of other orthostatic hypotensive conditions, including postural orthostatic tachycardia syndrome, in which there is autonomic dysfunction. The drug has been found to be effective and safe for both acute and chronic use, and it has minimal side effects.^{8,10,11} In patients

with massive hydrothorax, mild ascites, and no azotemia, the addition of midodrine to octreotide improves mean arterial pressure; increases the glomerular filtration rate, renal plasma flow, urine sodium levels, and urine volume; and prevents recurrence of hydrothorax. Vasoconstrictors have been recommended as treatment for hydrothorax, and these drugs have been found to be beneficial in refractory ascites.¹²⁻¹⁵

In our 2 patients, the addition of midodrine was found to be beneficial, with a decrease in both the frequency of LVP and the volume of ascitic fluid drained. This improvement occurred without a significant difference in the volume of fluid filtered by dialysis, despite improvements in blood pressure. It is possible that the beneficial effects of midodrine observed in our patients could be due to mechanisms other than the increase in blood pressure seen in patients with hydrothorax. Midodrine has been found to decrease nitrite and nitrate activity in patients with ascites with or without HRS who had decreased plasma renin activity and decreased levels of antidiuretic hormone.¹⁶ This could be a possible mechanism for decreasing portal pressure and decreasing ascitic fluid accumulation. There is also evidence that a similar reduction in fluid accumulation may occur with use of vasoconstrictors in patients with end-stage liver disease without a significant renal function improvement.^{17,18}

Midodrine is orally administered, easy to titrate, and has relatively few side effects. In our 2 patients, the beneficial effect on ascites occurred even when midodrine was used as a single agent, without another vasoconstrictor. In conclusion, the use of midodrine in appropriate patients with ascites and low systemic blood pressure may reduce the need for LVP, thus decreasing associated risks and improving patient comfort.

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Review

What is the Role of Midodrine in Patients with Decompensated Cirrhosis?

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Fluid accumulation and ascites are nearly universal in patients with decompensated liver disease, and their development in a cirrhotic patient generally portrays poor prognosis.^{1,2} The current hypothesis on the pathophysiology of ascites is that profound vasodilatation and hyperdynamic circulatory dysfunction induce reflex activation of the neurohormonal systems, nonosmotic release of antidiuretic hormone, and activation of the renin-angio-

tensin-aldosterone system (RAAS) with subsequent renal retention of sodium and water. Large-volume paracentesis (LVP), which removes at least 5 L of ascitic fluid, is used in patients with cirrhosis and tense ascites. When this treatment is used alone, it induces systemic vasodilatation and a decrease in effective arterial blood volume, and it is associated with impaired renal function and increased activity of the RAAS in approximately 80% of cases.³ Previous studies suggest that administration of a vasoconstrictor may be effective in preventing the hemodynamic alterations caused by paracentesis-induced circulatory dysfunction (PICD).^{4,6}

Midodrine hydrochloride, an α 1-agonist, increases effective circulating blood volume and renal perfusion by increasing systemic and splanchnic blood pressure.⁴ Midodrine is a prodrug that is absorbed from the gastrointestinal tract and metabolized by the liver into an active metabolite, desglymidodrine. Midodrine is an orally available, α -adrenergic agonist approved by the US Food and Drug Administration to treat symptomatic orthostatic hypotension. Investigations of midodrine alone or in combination have shown conflicting results for systemic and renal hemodynamics and renal function in patients with cirrhosis-related complications.⁷

Sourianarayanan and colleagues report the beneficial effect of midodrine in hypotensive cirrhotic patients with refractory ascites.⁸ One patient had been on hemodialysis for HIV-related nephropathy. The other patient had hepatorenal syndrome (HRS) requiring hemodialysis. In both cases, midodrine was apparently initiated to treat

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Table 1. Summary of Select Studies Using Midodrine for Various Indications in Patients with Liver Cirrhosis

Indication	Reference	Concomitant drugs	Results
Type 1 HRS	Angeli P, et al ¹⁰	Octreotide, albumin	Effective
	Wong F, et al ¹¹	Octreotide, albumin	Reduction of serum creatinine level
Type 2 HRS	Angeli P, et al ⁹		Modest effect on SH No effect on RF
Natriuretic effect	Kalambokis G, et al ⁵		Improved SH and sodium excretion
	Misra VL, et al ¹³	IV furosemide	No increase in natriuretic response to furosemide
PICD	Singh V, et al ⁶		As effective as albumin
	Appenrodt B, et al ¹²		Not as effective as albumin
Refractory ascites	Tandon P, et al ⁴	Octreotide, albumin	Reduction in the volume of ascites removed No effect on RF Reversible deterioration in MELD score
Post-LT renal outcomes	Rice JP, et al ¹⁴	Octreotide, albumin	Pre-LT treatment did not have superior post-LT renal function

HRS=hepatorenal syndrome; IV=intravenous; LT=liver transplantation; MELD=Model for End-Stage Liver Disease; PICD=paracentesis-induced circulatory dysfunction; RF=renal function; SH=systemic hemodynamic.

hypotension. In these 2 patients, the addition of midodrine was found to be beneficial, causing a decrease in both the frequency of LVP and the volume of ascitic fluid drained. However, the report is unclear about the starting dose for the first patient and how it was titrated upward. In addition, the report does not address why different doses were given to these 2 patients. Furthermore, we do not know if these patients experienced any side effects from midodrine.

Angeli and colleagues were the first to report the utility of midodrine to treat renal dysfunction in patients with cirrhosis.⁹ Their results suggest that oral administration of midodrine is associated with significantly improved systemic hemodynamics in nonazotemic cirrhotic patients with ascites.⁹ In patients with type 2 HRS, however, midodrine has modest effects on systemic hemodynamics and no effect on renal hemodynamics or renal function. A subsequent study showed that long-term administration of midodrine in combination with octreotide is safe and effective in individuals with type 1 HRS.¹⁰ In another study, a combination of midodrine, octreotide, and albumin was administered until the serum creatinine level was below 1.5 mg/dL for at least 3 days. This endpoint was achieved in 70% of patients with type 1 HRS.¹¹

Administration of a vasoconstrictor may be a viable therapeutic approach for improving the systemic and splanchnic vasodilatation involved in PICD.³ Kalambokis and colleagues reported the effects of a 7-day treatment

with midodrine in nonazotemic cirrhotic patients with and without ascites.⁵ Midodrine was administered at a dose of 10 mg TID for 7 days and was found to improve systemic hemodynamics and increase natriuresis in these patients. In patients with ascites, but not those without ascites, these effects were associated with a suppression of RAAS activity, suggesting that improvement in sodium excretion is related to improvement in effective arterial blood volume.

Two studies compared midodrine to intravenous albumin for preventing PICD in patients with cirrhosis and refractory ascites.^{6,12} In a study of 24 patients, 11 patients were randomized to receive midodrine administered at a dose of 12.5 mg every 8 hours for 2 days following 8 L of paracentesis.¹² Compared to patients who received albumin (n=13), more patients in the midodrine group had PICD, suggesting that midodrine is not necessarily effective in preventing circulatory dysfunction following LVP. However, another study showed that midodrine is as effective as intravenous albumin if its dose is titrated to maintain adequate blood pressure.⁶ In this study, midodrine was administered at a dose of 5–10 mg every 8 hours to maintain a mean arterial pressure 10 mmHg above baseline for 72 hours.

Another study investigated the effect of a 1-month course of therapy with midodrine, octreotide-LAR, and albumin in patients with refractory ascites.⁴ The authors observed a significant reduction in plasma renin and

aldosterone concentration and a trend toward a reduction in the volume of ascitic fluid removed by paracentesis without an effect on renal function. However, there was deterioration in Model for End-Stage Liver Disease scores during treatment due to a reversible increase in international normalized ratio and a trend toward an increase in bilirubin level.

Upon surveying the literature, it appears that midodrine has been explored for many indications in patients with cirrhosis; in large part, however, studies have yielded conflicting results, making it difficult to definitively conclude what role midodrine should play in this patient population (Table 1).^{4,6,9-14} In our practice, we consider midodrine therapy for cirrhotic patients with persistently low blood pressure (systolic pressure <90 mmHg) and patients with early type 1 HRS. When we administer midodrine for patients with type 1 HRS, we administer it in combination with octreotide and albumin. Based upon our anecdotal experience, as well as our interpretation of the published literature, midodrine is not useful to prevent PICD or to improve the natriuretic effect of loop diuretics. Rigorous studies are needed to investigate the precise role of this drug in the management of complications related to cirrhosis; unfortunately, funding agencies and the pharmaceutical industry traditionally have not invested in the management of end-stage liver disease.

This commentary was supported in part by a HAESF Senior Leaders & Scholar Fellowship to Dr. Werling.

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