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# It is reasonable to treat patients with type 1 hepatorenal syndrome with midodrine and Octreotide

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**ABSTRACT** A critical appraisal and clinical application of Esrailian E, Pantangco ER, Kyulo NL, Hu KQ, Runyon BA. Octreotide/midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. *Dig Dis Sci.* 2007;52(3):742-748. doi: [10.1007/s10620-006-9312-0](https://doi.org/10.1007/s10620-006-9312-0)

**Keywords:** hepatorenal syndrome, midodrine, octreotide, terlipressin, albumin, cirrhosis, ascites, acute kidney injury, creatinine

## Clinical Context

A 57 year old woman with a history of alcoholic cirrhosis presents to the emergency department with severe abdominal pain and distention. Over the past year, her ascites has been well controlled on home doses of furosemide and spironolactone. Only recently did she begin requiring therapeutic paracenteses, the last of which was just over a week ago. On admission, she was found to have acute kidney injury (AKI), with her serum creatinine at 7.2 mg/dL, up from a normal baseline ten days ago. Other causes of AKI were quickly ruled out, and she was diagnosed with type 1 hepatorenal syndrome (HRS). The patient was very concerned about her worsening kidney function, but she did not want to be started on dialysis. She wanted to know if there are any minimally invasive treatment options to improve her chances of survival until she becomes eligible for liver transplantation.

## Clinical Question

Are there any minimally invasive treatment options that improve survival in patients with type 1 hepatorenal syndrome in the United States?

## Research Article

Esrailian E, Pantangco ER, Kyulo NL, Hu KQ, Runyon BA. Octreotide/midodrine therapy significantly improves renal function and 30-day survival in patients with type 1 hepatorenal syndrome. *Dig Dis Sci.* 2007;52(3):742-748. doi: [10.1007/s10620-006-9312-0](https://doi.org/10.1007/s10620-006-9312-0)

## Literature Review

Hepatorenal syndrome is a well-recognized clinical entity of renal impairment secondary to portal hypertension in chronic liver disease, resulting from splanchnic vasodilation and compensatory renal vasoconstriction.<sup>1</sup> It occurs in up to 39% of patients with cirrhosis and ascites, and is associated with an extremely poor prognosis. Type 1 hepatorenal syndrome is a more severe and rapid

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entity, with most patients dying within weeks without treatment.<sup>2</sup> In addition to improvement of the underlying liver disease, current therapies have focused on reversal of splanchnic vasodilation and intravascular volume expansion in order to preserve renal perfusion and function.<sup>3,4</sup>

A review of the literature surrounding hepatorenal syndrome's therapies was performed using Cochrane Review and Ovid MEDLINE®. Meta-analyses and systematic reviews were identified and investigated for sources of primary literature examining therapeutic interventions for type 1 HRS. While several randomized controlled trials outline the benefits of terlipressin or terlipressin plus albumin in type 1 HRS, these were excluded due to the unavailability of terlipressin in the United States.<sup>3,4</sup> Other prospective studies supporting solely albumin for plasma expansion were not chosen due to their small population size.<sup>5,6</sup> Another prospective study evaluating the efficacy of midodrine plus octreotide versus dopamine was discounted due to its results not having achieved significance.<sup>7</sup> Studies involving renal replacement therapy, TIPS procedure, and liver transplantation were also excluded because of their invasive nature.<sup>8,9,10,11</sup>

Ultimately, a retrospective study by Esrailian et al. of patients with type 1 hepatorenal syndrome receiving treatment with midodrine and octreotide was chosen for critical appraisal and clinical application. This study had the advantage of being the largest single-study analysis of minimally invasive type 1 HRS therapy available to patients within the United States. It also provided similar results to the previously mentioned prospective study of midodrine plus octreotide therapy, but offered a larger patient base, thus allowing its results to achieve significance.

## Critical Appraisal

The article by Esrailian et al. is a well-executed retrospective analysis of 81 patients with type 1 HRS at Rancho Los Amigos Medical Center in Downey, California. The research method was a natural experiment, comparing similar patients, with therapy determined by the service, in the Medical Center, to which the patient was admitted. Sixty of these patients fell within the treatment group, having received therapy with oral midodrine and subcutaneous octreotide titrated to an increase in mean arterial pressure (MAP) by at least 15 mmHg during their admission. These patients were compared to 21 untreated type 1 HRS controls, who were concurrently admitted within the same time period. Because the group sizes are unequal, there is a potential selection bias. Inclusion criteria for both groups were taken from the widely-accepted International Ascites Club's diagnostic criteria for type 1 HRS, which involves demonstration of serum creatinine >1.5 mg/dL despite diuretic withdrawal and plasma volume expansion, as well as exclusion of other etiologies of renal impairment (shock, infection, nephrotoxic agents, etc.).<sup>1</sup> All patients received an average of 120g of albumin for plasma volume expansion in order to make this diagnosis; however, the only statistically significant difference in intervention was the octreotide and midodrine administration.

Primary endpoints included sustained reduction in serum creatinine, defined as serum creatinine <1.5 mg/dL for the duration of inpatient hospitalization, and survival at 30 days, defined as an outcome other than death (including discharge, TIPS procedure, liver transplantation, and leaving against medical advice with follow-up visit documenting survival). At thirty days, 71% (15/21) of patients within the control group had died, compared to only 43% (26/60) of patients within the treatment group—a statistically significant result ( $p < 0.05$ ). Thus, the treatment's absolute risk reduction of death was 28%, yielding a remarkably low number needed to treat of 3.56. Furthermore, after performing a multivariate analysis to control for any potential confounding factors, midodrine and octreotide treatment again produced a statistically significant increase in 30-day survival with an odds ratio of 4.41 ( $p = 0.02$ ).

This article has many strengths. First of all, the patient demographics and clinical presentations were similar between the treatment and control groups. Variables such as age, gender, ethnicity, liver disease etiology and severity, and initial serum creatinine were not significantly different. The only statistically significant distinction between the two groups was the serum albumin value, which was actually higher in the control group. Given that other studies have suggested the benefits of albumin administration in HRS<sup>5,6</sup>, this difference could have been expected to improve outcomes in the control group. The article also does an excellent job of selecting clinically relevant outcomes. In a condition such as type 1 HRS with median survival of two weeks<sup>2</sup>, patients and physicians should be primarily focused on short term survival—aptly designated as 30 days from treatment initiation in this study. Furthermore, the treatment regimen is feasible to implement—midodrine and octreotide are widely available across the United States, easily administered as oral and subcutaneous therapies, respectively.



This article does, however, have limitations. Its unblinded, nonrandomized, retrospective design is a principal source of bias that must be recognized. Consequently, its level of evidence is only 2b in accordance with Oxford Centre for Evidence-based Medicine. However, given the relative rarity of type 1 HRS and general lack of evidence surrounding available U.S. medical management options, this study's comparatively large sample size and significant results make a more convincing case than other smaller prospective studies that have been unable to achieve significance. Ultimately, bias will remain a risk until a randomized controlled trial can be performed, which the authors recognize. Furthermore, the primarily Hispanic male patient population is not entirely applicable to the predominantly African-American population served in Detroit. Methodologically, both groups were inevitably prescribed potentially confounding medications such as pentoxifylline that, although acknowledged in the article, are not explicitly recorded or analyzed as potential confounding factors. Additionally, a large number of patients were lost to follow-up at three and six months, making long-term effects on morbidity and mortality difficult to assess. However, again, with such a high short-term mortality in type 1 HRS, a significant survival difference at 30 days is clinically important.

Despite these limitations, this retrospective analysis by Esrailian et al. remains the most promising evidence for a minimally invasive treatment option for type 1 HRS accessible to patients within the United States. Its significant results, with well-controlled confounding variables, are clinically persuasive, although more work must be done. A randomized, controlled trial will be required to better substantiate the efficacy of midodrine and octreotide therapy.

### Clinical Application

Although a non-Hispanic Caucasian female, my patient was similarly admitted to a large teaching hospital within the United States and met the strict criteria for a diagnosis of type 1 HRS. As with the patients studied by Esrailian et al., she initially received albumin for plasma volume expansion, and was subsequently continued on nine days of midodrine and octreotide therapy resulting in a steady reduction of her serum creatinine down to a near-normal baseline of 1.5 mg/dL. Patients outside the United States may benefit from other therapies such as terlipressin, and patients in unstable conditions may require more urgent, invasive treatment options such as dialysis or a TIPS procedure. Nevertheless, my patient was transferred to a sub-acute rehabilitation facility in stable condition, and 23 days after treatment initiation, is alive, well, and preparing for future liver transplantation.

#### Take Home Points:

- 1.) In addition to treatment of the underlying liver disease, medical management of type 1 HRS with midodrine and octreotide is probably effective and currently the best-studied option available within the United States. Future randomized controlled trials studying midodrine and octreotide will aid in further elucidating the regimen's efficacy.
- 2.) The case described is similar to patients described in the paper appraised and can be considered a case report that adds to our knowledge of treating a deadly condition.
- 3.) Based on my experience and review of the literature, I would use midodrine and octreotide in a similar clinical scenario in the future.

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