# Dopamine and Furosemide for the Treatment of Hepatorenal Syndrome: A Reappraisal or Just Smoke and Mirrors?

Patients with advanced cirrhosis have a high to develop extrahepatic organ failures. Renal failure is common in patients with advanced cirrhosis and hepatorenal syndrome (HRS) represents the most life-threatening type of renal failure in these patients.[1] Until 30 years ago, no effective treatment of HRS was available and short-term mortality was almost 100% in these patients.[2] With the advent of orthotopic liver transplantation (OLT), HRS became an indication to OLT since it was shown that HRS resolved in most of the liver transplant recipients with a deep impact on survival.[3] Although OLT currently represents the treatment of choice for patients with HRS, organ shortage, and contraindication to OLT led scientists to look for medical treatments of HRS. In the last 20 years, the use of vasoconstrictors plus albumin showed to be effective in the treatment of HRS.[4–7] Among vasoconstrictors, terlipressin has been shown to be the most effective treatment of HRS and is currently considered the treatment of choice in many countries.[8,9] Other strategies, such as the use of vasodilators and or diuretics, were investigated with disappointing results. Indeed, the administration of dopamine showed to be uneffective in patients with cirrhosis and type 1 HRS.[4] Furthermore, dopamine had no effects on plasma renin activity in these patients.[4] As far as the use of diuretics is concerned, we should recognize that their use has been avoided because the depletion of effective circulating volume represents the trigger of renal hypoperfusion in patients with cirrhosis and HRS[10] and diuretics may further decrease the effective circulating volume in these patients.

In the current issue of J Clin Exp Hepatol, Srivastava et al. investigated the combination of dopamine, albumin, and low dose of furosemide versus terlipressin plus albumin in the treatment of HRS.[11] The Authors enrolled 40 patients with type 1 HRS and 40 patients with type 2 HRS. The patients were treated for 5 days and the authors evaluated response to treatment according to urinary output and urinary sodium excretion. Similar increases in urinary output and urinary sodium excretion were found in patients assigned to receive terlipressin and albumin and in those assigned to receive dopamine, furosemide, and albumin. These observations led the authors to conclude that the combination of dopamine albumin and furosemide was as effective as terlipressin plus albumin in the treatment of HRS and should be considered as an alternative treatment of HRS.

Several potential limitations of this study need to be highlighted and we want to add a note of caution about the conclusions of the authors.

1) The increase of urinary output does not mean improvement of renal function. Indeed, the response to treatment was poor in both groups with type 1 HRS as showed by a nonsignificant reduction of serum creatinine (sCr) at the end of treatment. Unfortunately, data about response to treatment according to standard criteria (reduction of sCr to a value <1.5 mg/dl or a reduction of sCr of at least 50% from baseline with a final value higher than 1.5 mg/dl for complete and partial response, respectively) were lacking.
2) The increase in urinary sodium excretion found in patients assigned to triple therapy does not necessarily suggest an improvement in renal function, since the use of furosemide may justify an increase in sodium excretion by means of furosemide action on renal tubular cells. Conversely, the increase in urinary sodium excretion found in patients assigned to receive terlipressin and albumin is only a matter of increased glomerular filtration rate, since terlipressin has no action on sodium tubular reabsorption.
3) The decision to limit the treatment to 5 days may have led to underestimate the response to treatment that may occur later in patients treated with terlipressin.
4) The study was underpowered to detect the noninferiority of the combination of dopamine, furosemide, and albumin versus terlipressin and albumin in the treatment of type 1 HRS.

Furthermore, the low efficacy of terlipressin in this randomized controlled trial deserves some comments. Probably, both the dose and the duration of treatment with terlipressin and albumin were not optimal. The dose of terlipressin used in this study (0.5 mg every 6 h) is much lower than those provided in previous randomized controlled trial[5,6] and seems to be inadequate to counteract the arterial splanchnic vasodilation in a 24 h period. In fact, we should bear in mind the pharmacodynamics and pharmacokinetics of terlipressin and Escorsell et al. showed that after single dose of 1 mg of terlipressin, its effects on splanchnic system lasts 3 h and the effects of 0.5 mg may last even earlier. As a result, patients included in the study were potentially off treatment for 50% of time. Despite all these limitations, it is important to recognize that this is the first randomized controlled trial comparing terlipressin and albumin versus dopamine plus furosemide and albumin. Some interesting observations need to be

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*Abbreviations:* HRS: hepatorenal syndrome; KDIGO: Kidney Disease Improving Global Outcomes; OLT: orthotopic liver transplantation; sCr: serum creatinine

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highlighted. The most important is the significant reduction in plasma renin activity in patients treated with dopamine, furosemide, and albumin. This may represent the starting point for planning a larger study.

Indeed, new prospective studies are needed in this field, in order to optimize the treatment of HRS and the outcome of these patients. In recent years, our knowledge on the pathophysiology of HRS has been significantly improved and new treatments should be investigated accordingly. First of all, Ruiz del Arbol et al. in two pivotal studies showed that patients with decompensated cirrhosis, with or without spontaneous bacterial peritonitis, who developed HRS had a significant lower baseline cardiac output than those patients who did not develop HRS.[13,14] This finding highlights the crucial role of cardiac output impairment in the development of HRS. Cardiac output may be a potential target for the treatment of HRS, in particular considering that terlipressin reduces cardiac output in patients with cirrhosis.[15] Future randomized controlled clinical trials should investigate the potential use of dopamine or other positive inotropic drugs in combination with terlipressin and albumin in the treatment of HRS. Secondly, Boyer et al. found that higher the baseline sCr, lower the possibility to achieve response to treatment with terlipressin and albumin.[16] This finding, as well as the acceptance of Kidney Disease Improving Global Outcomes (KDIGO) criteria led experts in this field to remove any cutoff from the diagnosis of HRS in the setting of acute kidney injury.[17] It has been claimed that these new criteria may allow a prompt treatment of HRS improving outcomes, but future prospective studies should be performed to confirm this speculation. Thirdly, data on pharmacokinetics and pharmacodynamics of terlipressin suggest that continuous intravenous infusion may be more effective and tolerated than intravenous boluses in the treatment of HRS[12,18]; however, it should be proven in randomized controlled clinical trials. Finally, it has been observed that patients with HRS may have signs of renal parenchymal damage.[19] As a consequence, the potential benefit of diuretic treatment with furosemide or renal replacement therapy should be investigated in patients with HRS and volume overload and/or in nonresponders to terlipressin and albumin.

In conclusion, in the last 30 years, the independent research has significantly improved the management and prognosis of patients with HRS. Nevertheless, there is still a lot of work to do, several unmet needs should be addressed in these patients and new studies such as the one from Srivastava et al. are more than welcome in this field.



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