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a randomized controlled trial

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Dobutamine reverses the cardio-suppressive effects of terlipressin without improving renal function in cirrhosis and ascites: a randomised controlled trial

Running title: Dobutamine and terlipressin for renal failure in cirrhosis

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Abbreviations: Ang I, angiotensin I; Ang II, angiotensin II; AVP, arginine-vasopressin; CO, cardiac output; EDTA, Ethylenediaminetetraacetic acid; GFR, glomerular filtration rate; HRS, hepatorenal syndrome; IQR, interquartile ranges; MAP, mean arterial pressure; RAAS, renin-angiotensin-aldosteron system; RIA, radioimmunoassay; SD, standard deviations
Abstract

Aim: Acute kidney injury and hepatorenal syndrome (HRS) are frequent complications in patients with cirrhosis and ascites. First-line treatment is terlipressin, which reverses HRS in approximately 40% of patients but also lowers cardiac output (CO). We aimed to investigate whether reversing the cardio-suppressive effect of terlipressin with the β-adrenoceptor agonist dobutamine would increase CO and thereby the glomerular filtration rate (GFR).

Methods: We randomised twenty-five patients with cirrhosis, ascites and impaired renal function (2:2:1): Group A received terlipressin followed by add-on of dobutamine, Group B received dobutamine and terlipressin as monotherapies and Group C received placebo. Renal and cardiac functions were assessed during 8 clearance periods of 30 minutes, and concentrations of vasoactive hormones were measured.

Results: Dobutamine as a monotherapy increased CO (1.03 L/min, P<0.01) but had no significant effects on GFR. Renin (P<.05), angiotensin II (P<.005) and aldosterone (P<.05) increased after dobutamine infusion. Terlipressin as a monotherapy improved GFR (18.9 ml/min/m2, p=.005) and mean arterial pressure (MAP) (14 mmHg, P=.001) but reduced CO (-0.92 L/min, P<.005) and renin (P<.005). A combined treatment of dobutamine and terlipressin had a positive effect on CO (1.19 L/min, P<.05) and increased renin (P<.005), angiotensin II (P<.005) and aldosterone (P<.05), but it had no significant effects on MAP or GFR.

Conclusion: Dobutamine reversed the cardio-suppressive effect of terlipressin in cirrhosis, ascites and impaired renal function. However, dobutamine reduced peripheral vascular resistance, activated RAAS and did not improve GFR compared to terlipressin as a monotherapy. Therefore, dobutamine cannot be recommended in cirrhosis and ascites.

New & Noteworthy: This study shows that the cardio-suppressive effects of the vasopressin receptor agonist, terlipressin, can be reversed by dobutamine. This is a novel observation in patients with decompensated cirrhosis. Furthermore, we show that dobutamine reduced the peripheral vascular resistance, activated the renin-angiotensin-system while renal function was not further improved that by terlipressin alone.
Introduction

Ascites is one of the most common complications of liver cirrhosis(10) and has a five-year survival rate of around 30% from the primary event of ascites(13). Ascites due to cirrhosis is characterised by intense sodium and water retention largely driven by high activity of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, which further foster decreased renal perfusion and filtration.(8) The development of ascites and progression to acute kidney injury (AKI) and hepatorenal syndrome (HRS) are closely linked to portal hypertension, hyperdynamic circulation and impaired renal function in the absence of any other identifiable cause of renal pathology. (6, 8, 46) AKI occurs in around 20% of all hospital admissions among patients with cirrhosis and 25% of patients progress to HRS.(13) The median survival of HRS is low, and HRS is characterised as a prerenal failure that does not respond to volume expansion.(41) Most reviews and guidelines recommend terlipressin, a vasopressin V1 receptor agonist, in combination with albumin as first-line therapy for HRS.(1, 2, 10) Terlipressin in combination with albumin reverses HRS significantly more often compared to albumin alone, but the reversal rate is less than 40%(1). The beneficial effects of terlipressin are attributed to: a splanchnic vasoconstriction that improves the central vascular territory; an increase in mean arterial pressure (MAP); and a decrease of the RAAS, which leads to improved renal perfusion and glomerular filtration rate (GFR).(25) However, the splanchnic vasoconstriction and increased MAP also lead to increased cardiac afterload, which probably explains why terlipressin also decreases heart rate and cardiac output (CO).(24) Impaired cardiac reserve and low CO are associated with increased risk of HRS and mortality in patients with cirrhosis and ascites.(23, 38-40) The cardio-suppressive effect of terlipressin on CO may explain why HRS is irreversible in some patients. It is therefore likely that eliminating the decrease in CO may improve outcomes. Administration of noradrenaline has in smaller clinical studies been shown to increase MAP(20) and CO(16) with beneficial effects on HRS.(20) Terlipressin has primarily
affinity for V1 receptors that are found mainly on the vascular smooth muscle cells in the splanchnic circulation where it mediates selective splanchnic vasoconstriction. For these reasons, it seems rational to combine terlipressin with a drug, that increases CO(18, 25), which does not use the same target in the resistance vessels as terlipressin. Dobutamine is a sympathomimetic drug with strong affinity for β1- and less affinity for β2-receptors.(36)

Dobutamine effectively increases heart rate and CO in patients with cirrhosis.(7, 22) In patients with cirrhosis and in patients with low CO following acute myocardial infarction dobutamine increases the pulse pressure without affecting MAP.(7, 21) Dobutamine has also been found to counteract the cardio-suppressive effects of terlipressin in patients with septic shock.(32) It is, however, unclear whether dobutamine has beneficial effects on renal function in patients with cirrhosis and ascites. Furthermore, it is not known whether dobutamine can counteract the cardio-suppressive effects of terlipressin in cirrhosis and whether the combination has synergistic effects on renal function. We therefore hypothesised that the β-adrenoceptor agonist dobutamine would reverse the suppressive action of terlipressin on heart rate and CO and lead to improved renal function.
Materials and Methods

ETHICS

This study was performed according to ICH-GCP and the Declaration of Helsinki and approved by the Committee of Health Research Ethics in the Region of Southern Denmark. External monitoring was performed by Good Clinical Practice Unit at Odense University Hospital. The study is registered at the European Clinical Trials Register, EudraCT number: 2012-002275-33.

PARTICIPANTS

Patients with cirrhosis and ascites between age 18 and 75 were considered eligible for the trial. The diagnosis of cirrhosis was based on liver biopsy or presence of portal hypertension verified by liver vein catheterisation, gastro-oesophageal varices in combination with characteristic clinical and biochemical signs. Ascites was diagnosed based on paracentesis or abdominal ultrasonography within three months prior to inclusion. Ascites was an inclusion criterion to ensure that participants had functional renal impairment and associated sodium and water retention and consequently were comparable to patient with AKI-HRS. We excluded patients diagnosed with insulin-dependent diabetes mellitus and other causes of chronic kidney disease to ensure that the renal impairment was related to the underlying liver disease. Additional exclusion criteria were transjugular intrahepatic portosystemic shunt, ischaemic cardiac disease, congestive heart disease, chronic obstructive pulmonary disease and cancer, including hepatocellular carcinoma. Furthermore, pregnant patients, patients who were breastfeeding and patients suffering from overt hepatic encephalopathy were also excluded. For ethical and practical reasons, the study was performed on stable patients due to the comprehensive investigation program which required proper collaboration with the participants and investigators. Recruitment and investigations of all participants took place in the Department of Gastroenterology and Hepatology, Odense University Hospital, Denmark.
Patients who were considered eligible and who had given informed consent were included. Diuretics, beta-blockers, and other vasoactive drugs including blood pressure lowering drugs were discontinued 7 days prior to the investigations. After receiving oral and written instructions, all participants followed a sodium-restricted diet (60 mmol/day) for 7 days prior to the investigations. To characterise the fluid reabsorption rate in proximal tubule of the kidneys, lithium carbonate 300 mg was orally administered twelve hours before the investigations. The investigation started at 10.00 am after at least 10 hours of fasting. An oral load of 100 ml of tap water was provided every half hour from 9.00 am until the end of the investigations to ensure positive fluid balance with similar and low osmotic stimuli for endogenous vasopressin.

STUDY DESIGN AND INTERVENTION

The study was conducted as an investigator-initiated randomised placebo-controlled intervention trial in which we tested the renal and cardiac effects of dobutamine and terlipressin. Random numbers were generated by a computer, and opaque sealed envelopes were used to allocate the participants into the three groups in a ratio of 2:2:1. Figure 1 illustrates the study set-up. The Run-in period (60 minutes) was followed by three individual investigation periods: Baseline (60 minutes), Intervention 1 (90 minutes), and Intervention 2 (90 minutes). Renal investigations were performed every 30 minutes from Baseline to the end of the investigations. Cardiac and hormonal investigations were performed once for each period. We randomised the participants into the following groups: Group A received terlipressin followed by dobutamine; Group B received dobutamine followed by terlipressin; and Group C received saline as placebo.

Dobutamine was infused continuously starting at 10 µg/kg body weight/min and increased every 3 minutes by 10 µg/kg body weight/min until reaching the targeted heart rate or a max dose of 40 µg/kg body weight/min. Target heart rate was a 50% increase of resting heart rate or a maximum
heart rate of 120 beats per minute. Group A received dobutamine infusion during **Intervention 2**, and Group B received dobutamine infusion during **Intervention 1**. Dobutamine has a half-life of elimination of around two minutes (27). The treatment was stopped the last ten minutes of the period to ensure that dobutamine was eliminated at the entrance to the next period.

Terlipressin 2 mg in 10 ml (9 mg/ml) NaCl solution was administrated as a bolus injection over two minutes. Group A received an injection of terlipressin at the beginning of **Intervention 1** (Figure 1). Group B received an injection of terlipressin at the beginning of **Intervention 2**. The peak effect of terlipressin is reached 60 to 120 minutes after administration and the half-life of elimination is 50 minutes (25). Due to the prolonged half-life of terlipressin, we assumed that its effect would remain from injection until the end of study. Accordingly, Group A was treated with the combination of terlipressin and dobutamine during **Intervention 2**.

The placebo was 10 ml of 9 mg/ml NaCl. Group C received placebo injections over two minutes at the beginning of **Intervention 1** and **Intervention 2**.

**OUTCOME MEASUREMENTS**

The primary outcome measure was glomerular filtration rate (GFR). Other renal outcome measures were free water clearance, osmolar clearance and sodium-, potassium-, and lithium clearance. Cardiac measures were cardiac output, cardiac index, stroke volume and MAP. Vasoactive hormone measurements included levels of renin, angiotensin II (Ang II), aldosterone, and arginine-vasopressin (AVP).

**INVESTIGATION OF KIDNEY FUNCTION AND ELECTROLYTE HANDLING**

For the renal measurements, blood and urine samples were simultaneously taken every 30 minutes and urine volume was measured using a bladder catheter. We used $^{51}$Cr-EDTA clearance as reference substance to determine GFR. At the initiation of the run-in period, all participants had a
$^{51}$Cr-EDTA bolus injection followed by a constant infusion throughout the investigation. The
radioactivity of $^{51}$Cr-EDTA in blood and urine samples was assessed using a gamma counter
(Packard, Cobra Auto-Gamma). GFR was calculated and adjusted for body surface area. We used
lithium clearance to characterise the fluid reabsorption rate in a proximal tubule and the flow
entering the Loop of Henle based on the assumption that lithium is freely filtered in the glomerulus
and reabsorbed isosmotically along the proximal tubule with no further reabsorption when the fluid
enters the Loop of Henle. Lithium, sodium and potassium levels in blood and urine were measured
using a flame photometry (Packard, Cobra Auto-Gamma). We used a Single-Sample Osmometer
(Advanced Instruments) to obtain osmolarity measurements in blood and urine. Clearance
calculations were based on the standard formula: $C_x = V_u \times (U_x/P_x)$, where $C_x =$ renal clearance of
substance x, $V_u =$ urine flow rate, $U_x =$ urine concentration of substance x, and $P_x =$ plasma
concentration of substance x. The excretion fraction was calculated using the standard formula: $FE_x$
$= C_x/GFR$. Free water clearance was calculated using the standard formula: $C_{h2o} = V_u - C_{osm}$.

CARDIAC INVESTIGATIONS

Inert gas rebreathing method was used to non-invasively determine cardiac output and stroke
volume (Innocor®, Innovision ApS, Odense, Denmark).(5) Based on Fick’s principle, this
technique estimates cardiac output by measuring the relative levels of one blood soluble gas and
one insoluble gas that are rebreathed by the subject.(42) MAP was calculated: MAP=$1/3$*systolic
pressure + $2/3$*diastolic pressure. Twelve lead-ECG was recorded to evaluate arrhythmias and
ischemic changes.

HORMONES

Blood samples were collected in K2-EDTA tubes chilled in crushed ice. The tubes were centrifuged
immediately after sampling at 4° C. Plasma was pipetted in secondary tubes and stored at –80° C.
We analysed all samples in the same batch at the end of the study. Plasma renin concentrations were measured by radioimmunoassay (RIA) of Angiotensin I (Ang I) through the antibody-trapping method of Poulsen and Jørgensen.\(^\text{(37)}\) Between-assay coefficient of variation was 15%. Specific in-house antibodies were used to determine the concentration of Ang II and AVP.\(^\text{(4)}\) Ang II and AVP peptide hormone concentrations in plasma were measured by RIA using specific antibodies [Ab-5-030682] and antibody [AB3096]. The assay procedure leading to the RIA has previously been described in detail.\(^\text{(9)}\) Plasma aldosterone concentrations were measured using a commercial enzyme immunoassay kit ELISA (MS E-5200, Labor Diagnostika Nord GmbH & Co. KG, Germany). Human EDTA plasma pool was used as an internal standard (79 ± 8 pg/mL).

STATISTICS

We designed the study with a type I error of 0.05 and a power of 80% to detect a 20% difference in the primary outcome (GFR) between the interventions. In a paired design, eight participants are required in each group to detect a 20% difference in GFR\(^\text{(26)}\) and with a 20% standard deviation of GFR estimations,\(^\text{(26, 35)}\) we planned to enrol 10 participants in each group of active treatment. Based on previous studies using a similar design, we did not expect any changes in GFR in the placebo group.\(^\text{(26, 35)}\)

The descriptive data are reported here as counts and frequencies (%), means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on distribution. We report the statistical significance of between-group comparisons with the chi-square test for categorical data, one-way ANOVA for parametric, continuous data and the Kruskal Wallis test for non-parametric, continuous data. Relative changes for graphical illustrations were calculated by taking the mean and standard deviation of fold-change of each participant. Mean effects on cardiac and renal outcome
measurements were calculated using mixed model for repeated measurements. Effects on vasoactive hormone levels were tested using a Wilcoxon signed-rank test for paired non-parametric data. We used a significance level of 0.05. The statistical software STATA 15 (College Station, TX, US) was used for all calculations. If a urine sample had a volume <1 ml, the sample was merged with the next sample and a mean value was calculated and used for both periods.
Results

PARTICIPANT CHARACTERISTICS

From June 2014 to May 2018 we screened 245 patients with cirrhosis and ascites (Figure 2), 46 of which were eligible for the study. Twenty-seven agreed to participate and were included and randomised. Two participants experienced an adverse event between inclusion and the investigation, and they did not receive any study drugs. Twenty-five participants completed the study and were included for further analyses. Most of the participants were males with alcoholic liver cirrhosis (Table 1). Twenty-two participants received diuretics at inclusion for the management of ascites. Three participants did not receive diuretics due to a history of deterioration of renal function during diuretic treatment, a condition known as diuretic intractable ascites.\(^{(3, 10)}\)

The patient groups were identical with respect to demography, standard laboratory tests, and renal and cardiac parameters at baseline of the investigations (Table 1). The main effects of dobutamine and terlipressin are illustrated in Figure 3, which shows relative changes in GFR, CO, MAP and plasma renin concentrations. Table 2 shows cardiac and renal effects of dobutamine, terlipressin and interactions between the two drugs. Effects of dobutamine and terlipressin on the level vasoactive hormones are shown in Table 3.

EFFECTS OF DOBUTAMINE ON CARDIAC AND RENAL PARAMETERS

Dobutamine significantly increased cardiac output (+1.03 L/min, SE±0.39, P<0.01) and cardiac index (+0.58 L/min, SE±0.20, P<0.005) by increasing heart rate (+29 min\(^{-1}\), SE±3, P<0.001), while it also reduced stroke volume (-10.5 mL/beat, SE±4.9, P<0.05) (Figure 3/Table 2). Dobutamine had no significant effect on blood pressure, but there was a trend towards a lower diastolic blood
pressure (P=0.05, Table 2). Dobutamine increased free water clearance (+0.33 ml/min, SE±0.12, P<0.01) and tended to decrease GFR (-10.4 ml/min, SE±7.7, P=0.181). Renin (P<0.05), Ang II (P<0.005) and aldosterone (P<0.05) all increased, whereas arginine-vasopressin was not significantly affected (Table 3).

EFFECTS OF TERLIPRESSIN ON CARDIAC AND RENAL PARAMETERS

Terlipressin significantly decreased heart rate (-9 min⁻¹, SE±2, P<0.001), cardiac output (-0.92 L/min, SE±0.30, P<0.005) and cardiac index (-0.47 L/min, SE±0.16, P<0.005) (Figure 3/Table 2). Moreover, terlipressin significantly increased MAP (+14 mmHg, SE±4, P=0.001), systolic blood pressure and diastolic blood pressure (Table 2). Renal function was improved, including significant increases in GFR (+18.8 ml/min, SE±6.7, P=0.005), Na-, K- and Li-clearances (Figure 3/Table 2). There were borderline significant trends towards a higher osmolar clearance and a lower free water clearance (Table 2). Terlipressin decreased the renin concentration (p<0.005) but had no significant effect on Ang II or aldosterone. (Table 3).

EFFECTS OF ADDING DOBUTAMINE TO TERLIPRESSIN ON CARDIAC AND RENAL PARAMETERS

Co-treatment with dobutamine and terlipressin significantly increased heart rate and cardiac output (+1.19 L/min, SE±0.6, P<0.05) (Figure 3/4). No other interactions were observed between terlipressin and dobutamine with regard to renal outcomes (Table 2). Adding dobutamine to terlipressin increased plasma renin (P<0.005) and Ang II levels (P<0.005) (Table 3).
COMPLIANCE AND ADVERSE EVENTS

Overall, treatment was well tolerated and during dobutamine titration the target heart rate was reached in 19 of 20 patients who received active treatment. In the group who received dobutamine as a monotherapy, the mean heart rate was increased by 37% from a mean of 80 min\(^{-1}\) to 109 min\(^{-1}\) (Figure 4, Group B). Mean heart rate was increased by 47% from a mean of 76 min\(^{-1}\) to 111 min\(^{-1}\) in the group who received dobutamine as add-on to terlipressin (Figure 4, Group A). Milder side effects to treatment were observed in most of the participants (Table 4). One participant who received combined treatment experienced severe hypertension and consequently, dobutamine infusion was stopped and blood pressure normalised within ten minutes.
Discussion

This randomised controlled pilot trial addresses the circulatory and renal changes in patients with cirrhosis and ascites during renal impairment while undergoing treatment with terlipressin and dobutamine. Our main findings were: 1) Dobutamine infusion increased heart rate, increased CO and reversed the cardio-suppressive effects of terlipressin in patients with cirrhosis, ascites and impaired renal function; 2) Co-treatment with dobutamine and terlipressin did not increase MAP, nor did it translate into further increase in GFR; 3) Dobutamine infusion led to a significant increase in plasma renin, Ang II and aldosterone levels.

The pathophysiology leading to decreased GFR in the development of AKI-HRS comprises hemodynamic derangement with impaired cardiac reserve, low MAP and activation of the RAAS(15). Our study showed that the beneficial effect of terlipressin on GFR is closely linked to an increase of MAP and decrease in renin levels, which is in line with earlier studies.(24, 44) Our findings also confirmed that terlipressin has a cardio-suppressive effect, but as a more novel and important finding, our study proved that the cardio-suppressive effect of terlipressin is reversible. However, the increased cardiac function did not translate into an increase of GFR. Dobutamine was applied to reverse the cardio-suppressive effect of terlipressin, which increased heart rate by > 35 % and led to a significantly higher CO. Surprisingly, the increase in CO was not accompanied by a rise in MAP, most likely because dobutamine induces a reduction in peripheral vascular resistance mediated by beta-adrenergic stimulation.

Another interesting observation was that dobutamine increased plasma levels of all components of RAAS, which is in line with previous findings in experimental studies on healthy subjects and patients with chronic heart disease.(21, 34, 45) Progressive levels of renin are regarded as a marker
of circulatory dysfunction and renal impairment in cirrhosis. All patients in the study had ascites and renal impairment with the associated high plasma levels of renin, Ang II and aldosterone compared with healthy individuals. Moreover, plasma renin levels are very dynamic and mirror the response to terlipressin regarding improvement of GFR and reversal of acute kidney injury and HRS. Consistent with this, we observed that improved GFR was related to decreased plasma renin levels in patients who received terlipressin. Dobutamine infusion was found to affect the RAAS activity and increased the levels of renin, Ang II and aldosterone. Animal studies suggest that renin secretion is suppressed in β1-adrenoreceptor-deficient mice, indicating that renin-producing cells in the kidneys express β1-adrenoreceptors. Our results support that dobutamine is a potent β1-adrenoreceptor agonist that stimulates the renin-producing cells in the kidneys. Renin secretion is considered the rate-limiting factor in RAAS activation that governs formation of the effector molecules Ang II and aldosterone. Some studies suggest that because the renin substrate angiotensinogen is reduced in patients with decompensated cirrhosis, renin secretion may not lead to increased levels of Ang II and aldosterone. However, our data indicate that the synthesis of angiotensinogen was sufficient because the dobutamine-induced renin secretion was accompanied by increased levels of Ang II and aldosterone. Ang II is a potent endogenous vasoconstrictor that increases intrarenal vascular tone and reduces renal perfusion in patients with cirrhosis and ascites. Taken together, the vascular effects of dobutamine probably lead to reduced renal perfusion because of decreased peripheral vascular resistance combined with intrarenal vasoconstriction induced by RAAS activation. This reduced renal perfusion may explain why dobutamine as monotherapy and in combination with terlipressin increases CO without translating into an improved GFR.
Terlipressin and dobutamine affect CO, peripheral vascular resistance and RAAS in opposite directions and in line with that, the combined treatment does not result in any significant improvement in GFR compared to terlipressin as a monotherapy. The treatment duration was relative short compared with treatment of AKI-HRS in clinical practice.(10) Based on the results from present study, we cannot conclude that changes in vasoactive substances and their subsequent effects on renal perfusion were fully pronounced after 90 minutes of treatment. However, it seems most likely, that the effect of dobutamine leading to activation of RAAS was pronounced and will persist in prolonged treatment, considering that renin has a half-life less than 15 minutes(43) and angiotensin II less than 1 minute(31). Due to the study design with a comprehensive investigation program aiming at providing mechanistic insight and proof of concept, it was not feasible to include patients with AKI-HRS and study clinical endpoints, which may limit the generalisation of our findings in a clinical context. Thus, we cannot exclude, that patients with AKI-HRS will respond differently and long-term treatment may surface further pharmacodynamics effects. However, at this point it seems most likely that the vascular effects of dobutamine are undesirable in the management of AKI-HRS and further clinical testing should be performed with great caution. It should be emphasized that several clinical trials have reported that patients in whom terlipressin leads to increased MAP and decreased levels of renin seem more likely to benefit from treatment.(30, 33) The mechanisms of action of terlipressin and dobutamine may be different in other conditions like septic shock with separate pathophysiology and our results may therefore not be transferrable outside cirrhosis and ascites.(29)It should also be noted that despite randomisation and no statistical differences, Group C had higher levels of vasoactive hormones at baseline. However, all outcomes were stable in Group C during the investigation including vasoactive hormones, and therefore it seems reasonable to use Group C as controls.
In conclusion, this study demonstrates that it is possible to reverse the cardio-suppressive effects of terlipressin in patients with cirrhosis and ascites and that patients tolerate the combined treatment well. However, dobutamine reduces peripheral vascular resistance and activates RAAS and does not additionally improve GFR in patients with cirrhosis and ascites compared to terlipressin alone. Dobutamine does not seem to potentiate the renal effects of terlipressin and therefore cannot be recommended in clinical practice or further testing in patients with cirrhosis and ascites.
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Conflict of interests: The authors of presents study have no conflicting interests to declare
REFERENCES


Figure legend

Figure 1: Study investigation overview.
During “Run in” plasma levels of 51Cr-EDTA were stabilised.

Figure 2: Trial profile.
*Other = non-HCC cancer, low compliance and dementia. Age>75 = Age above 75 years, HCC = Hepatocellular carcinoma, TIPS = Transjugular intrahepatic portosystemic shunt, IHD = ischemic heart disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, CKD = Chronic kidney disease, IDDM = insulin-dependent diabetes mellitus.

Figure 3: Relative effects of dobutamine and terlipressin by group.
Terli = terlipressin; Dobu = dobutamine; GFR = glomerular filtration rate; PRC = plasma renin concentration; CO = cardiac output; MAP = mean arterial pressure; SD = standard deviation.

Figure 4: Mean heart rate during baseline investigations and intervention period 1 and 2.
Terli = Terlipressin, Dobu = dobutamine, min^-1 = min^{-1}
Table 1: Participant characteristics

<table>
<thead>
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<th>Demography</th>
<th>Overall N=25</th>
<th>Group A N=10</th>
<th>Group B N=10</th>
<th>Group C N=5</th>
<th>P-value</th>
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<td>Gender (male)</td>
<td>17 (68%)</td>
<td>7 (70%)</td>
<td>6 (60%)</td>
<td>4 (80%)</td>
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<td>Age (years)</td>
<td>56.6 (± 8.8)</td>
<td>58.8 (± 9.9)</td>
<td>54.4 (± 7.7)</td>
<td>56.4 (± 9.5)</td>
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<td>Aetiology (Alcohol)</td>
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<td>9 (90%)</td>
<td>9 (90%)</td>
<td>5 (100%)</td>
<td>1.000</td>
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<td>Diuretic treatment (yes)</td>
<td>22 (88%)</td>
<td>10 (100%)</td>
<td>8 (80%)</td>
<td>4 (80%)</td>
<td>0.391</td>
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<td>Spironolactone (mg/day)</td>
<td>95 (±80)</td>
<td>105 (±76)</td>
<td>82.5 (±90)</td>
<td>100 (±82)</td>
<td>0.882</td>
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<tr>
<td>Furosemide (mg/day)</td>
<td>37 (±39)</td>
<td>42 (±30)</td>
<td>27 (±47)</td>
<td>50 (±38)</td>
<td>0.035</td>
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<tr>
<td>β-blocker treatment (yes)</td>
<td>8 (32%)</td>
<td>4 (40%)</td>
<td>2 (20%)</td>
<td>2 (40%)</td>
<td>0.634</td>
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<tr>
<td>P-Creatinine (µmol/L; 60–130)</td>
<td>81 (±22)</td>
<td>85 (±22)</td>
<td>74 (±19)</td>
<td>85 (±27)</td>
<td>0.517</td>
</tr>
<tr>
<td>P-Na (mmol/L; 136–146)</td>
<td>136 (±4.3)</td>
<td>138 (±4.1)</td>
<td>135 (±4.2)</td>
<td>134 (±5.0)</td>
<td>0.283</td>
</tr>
<tr>
<td>P-K (mmol/L; 3.5–4.4)</td>
<td>4.1 (±0.4)</td>
<td>4.0 (±0.4)</td>
<td>4.2 (±0.4)</td>
<td>4.1 (±0.5)</td>
<td>0.584</td>
</tr>
<tr>
<td>P-albumin (g/L; 36-45)</td>
<td>33 (±5.6)</td>
<td>36 (±6.0)</td>
<td>30 (±5.0)</td>
<td>33 (±3.3)</td>
<td>0.162</td>
</tr>
<tr>
<td>Ascites (grade 0/1/2/3)</td>
<td>0/1/18/6</td>
<td>0/0/8/2</td>
<td>0/1/7/2</td>
<td>0/0/3/2</td>
<td>0.707</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>8.7 (±0.3)</td>
<td>8.4 (±0.5)</td>
<td>9.1 (±0.4)</td>
<td>8.6 (±0.7)</td>
<td>0.583</td>
</tr>
<tr>
<td>MELD-Na</td>
<td>12.3 (±5.5)</td>
<td>10.4 (±3.7)</td>
<td>14.4 (±7.0)</td>
<td>12.0 (±4.6)</td>
<td>0.800</td>
</tr>
</tbody>
</table>

Cardiovascular function

<table>
<thead>
<tr>
<th></th>
<th>Overall N=25</th>
<th>Group A N=10</th>
<th>Group B N=10</th>
<th>Group C N=5</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (L/min)</td>
<td>7.2 (±0.4)</td>
<td>6.6 (±0.3)</td>
<td>8.1 (±0.9)</td>
<td>6.3 (±0.7)</td>
<td>0.158</td>
</tr>
<tr>
<td>Cardiac index (L/min/1.73 m²)</td>
<td>3.7 (±0.2)</td>
<td>3.5 (±0.2)</td>
<td>4.1 (±0.4)</td>
<td>3.3 (±0.3)</td>
<td>0.181</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>84 (±14)</td>
<td>87 (±14)</td>
<td>80 (±14)</td>
<td>86 (±14)</td>
<td>0.513</td>
</tr>
<tr>
<td>Ejection volume (ml/beat)</td>
<td>89 (±7)</td>
<td>75 (±6)</td>
<td>105 (±12)</td>
<td>82 (±10)</td>
<td>0.085</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>95 (±10)</td>
<td>97 (±8)</td>
<td>94 (±13)</td>
<td>91 (±8)</td>
<td>0.516</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>133 (±3)</td>
<td>135 (±4)</td>
<td>135 (±7)</td>
<td>125 (±4)</td>
<td>0.449</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76 (±2)</td>
<td>79 (±3)</td>
<td>74 (±3)</td>
<td>74 (±4)</td>
<td>0.487</td>
</tr>
</tbody>
</table>

Renal function

<table>
<thead>
<tr>
<th></th>
<th>Overall N=25</th>
<th>Group A N=10</th>
<th>Group B N=10</th>
<th>Group C N=5</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>46.9 (±27.1)</td>
<td>42.6 (±23.2)</td>
<td>51.57 (±31.0)</td>
<td>46.3 (±30.84)</td>
<td>0.775</td>
</tr>
<tr>
<td>Osmolar clearance (ml/min)</td>
<td>1.3 (±0.8)</td>
<td>1.3 (±0.7)</td>
<td>1.6 (±1.0)</td>
<td>1.0 (±0.4)</td>
<td>0.380</td>
</tr>
<tr>
<td>Free-water clearance (ml/min)</td>
<td>-0.6 (±0.1)</td>
<td>-0.5 (±0.1)</td>
<td>-0.7 (±0.3)</td>
<td>-0.4 (±0.2)</td>
<td>0.672</td>
</tr>
<tr>
<td>U-Na (mmol/L)</td>
<td>51 (10-107)</td>
<td>60 (10-109)</td>
<td>69 (10-123)</td>
<td>5 (1-51)</td>
<td>0.182</td>
</tr>
<tr>
<td>Na-clearance (ml/min)</td>
<td>0.4 (±0.1)</td>
<td>0.4 (±0.1)</td>
<td>0.6 (±0.2)</td>
<td>0.1 (±0.1)</td>
<td>0.231</td>
</tr>
<tr>
<td>U-K (mmol/L)</td>
<td>57 (50-89)</td>
<td>62 (51-121)</td>
<td>55 (40-83)</td>
<td>68 (51-97)</td>
<td>0.569</td>
</tr>
<tr>
<td>K-clearance (ml/min)</td>
<td>10.5 (±1.5)</td>
<td>11.9 (±2.7)</td>
<td>11.4 (±2.4)</td>
<td>6.0 (±1.5)</td>
<td>0.319</td>
</tr>
</tbody>
</table>

Hormones

<table>
<thead>
<tr>
<th></th>
<th>Overall N=25</th>
<th>Group A N=10</th>
<th>Group B N=10</th>
<th>Group C N=5</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin (mIU/L)</td>
<td>103 (39-257)</td>
<td>95 (39-140)</td>
<td>86 (12-206)</td>
<td>510 (109-1109)</td>
<td>0.208</td>
</tr>
<tr>
<td>Angiotensin II (pg/mL)</td>
<td>29 (12-46)</td>
<td>30 (16-40)</td>
<td>19 (±8.29)</td>
<td>142 (42-201)</td>
<td>0.121</td>
</tr>
<tr>
<td>Aldosterone (pg/mL)</td>
<td>390 (151-702)</td>
<td>531 (125-619)</td>
<td>203 (151-554)</td>
<td>1082 (295-2403)</td>
<td>0.440</td>
</tr>
<tr>
<td>Arginine-Vasopressin (pg/mL)</td>
<td>1.99 (1.50-3.74)</td>
<td>2.04 (1.82-3.58)</td>
<td>1.65 (0.91-2.85)</td>
<td>3.36 (2.73-3.90)</td>
<td>0.247</td>
</tr>
</tbody>
</table>

Counts are presented as N (%), parametric continuous data are presented as Mean (±SD), non-parametric continuous data as medians (IQR). P-Crea, Plasma creatinine; P-Na, Plasma sodium; P-K, Plasma potassium; P-Alb, Plasma albumin; U-Na, Urine sodium; U-K, Urine potassium; C-P, Child-Pugh; MELD-Na, Model for End-Stage Liver Disease; GFR, Glomerular filtration rate; CO, Cardiac output; HR, Heart rate; MAP, Mean arterial pressure; PRC, Plasma renin count.
<table>
<thead>
<tr>
<th></th>
<th>Dobutamine</th>
<th>Terlipressin</th>
<th>Terlipressin+Dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>1.03 (0.26 to 1.80) **</td>
<td>-0.92 (-1.52 to -0.32)**</td>
<td>1.19 (0.01 to 2.38)*</td>
</tr>
<tr>
<td>Cardiac index (L/min/1.73 m²)</td>
<td>0.58 (0.18 to 0.97)**</td>
<td>-0.47 (-0.77 to -0.16)**</td>
<td>0.57 (-0.04 to 1.17)</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>28.6 (23.6 to 33.5)**</td>
<td>-9.3 (-13.1 to -5.5)**</td>
<td>6.09 (-1.2 to 13.4)</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>-10.5 (-20.0 to -0.9) *</td>
<td>0.2 (-7.2 to 7.6)</td>
<td>6.9 (-7.8 to 21.5)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>-5.0 (-13.8 to 3.7)</td>
<td>13.9 (5.8 to 21.9)**</td>
<td>3.7 (-7.0 to 14.3)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>-4.5 (-21.4 to 12.3)</td>
<td>21.0 (5.4 to 36.5)**</td>
<td>9.9 (-10.3 to 30.2)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>-6.0 (-12.1 to 0.1)</td>
<td>9.4 (3.9 to 15.0)**</td>
<td>1.1 (-6.5 to 8.7)</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min/1.73m2)</td>
<td>-10.4 (-25.5 to 4.8)</td>
<td>18.8 (5.7 to 32.0)**</td>
<td>9.0 (-11.1 to 29.2)</td>
</tr>
<tr>
<td>Osmolar clearance (ml/min)</td>
<td>-0.18 (-0.62 to 0.25)</td>
<td>0.36 (-0.02 to 0.75)</td>
<td>-0.17 (-0.73 to 0.38)</td>
</tr>
<tr>
<td>Free water clearance (ml/min)</td>
<td>0.33 (0.09 to 0.57)**</td>
<td>-0.19 (-0.40 to 0.02)</td>
<td>-0.25 (-0.56 to 0.06)</td>
</tr>
<tr>
<td>Na-clearance (ml/min)</td>
<td>-0.01 (-0.14 to -0.13)</td>
<td>0.12 (0.01 to 0.24)*</td>
<td>-0.10 (-0.26 to 0.07)</td>
</tr>
<tr>
<td>K-clearance (ml/min)</td>
<td>-0.53 (-4.56 to 3.49)</td>
<td>6.78 (2.97 to 10.59)**</td>
<td>1.69 (-6.59 to 3.21)</td>
</tr>
<tr>
<td>Li-clearance (ml/min)</td>
<td>1.12 (-4.31 to 6.55)</td>
<td>7.05 (1.98 to 12.13)**</td>
<td>-3.92 (-10.41 to 2.57)</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate. 95% confidence intervals are presented in parentheses. * = p-values < 0.05 and ** p-values < 0.01
**TABLE 3: Effects of dobutamine and terlipressin on the level vasoactive hormones**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Period 1</td>
<td>Period 2</td>
</tr>
<tr>
<td>Renin (mIU/L)</td>
<td>95</td>
<td>48**</td>
<td>2377**##</td>
</tr>
<tr>
<td>ANG II (pg/mL)</td>
<td>30</td>
<td>22</td>
<td>64**##</td>
</tr>
<tr>
<td></td>
<td>(16-40)</td>
<td>(9-29)</td>
<td>(35-91)</td>
</tr>
<tr>
<td>Aldo (pg/mL)</td>
<td>531</td>
<td>486</td>
<td>460##</td>
</tr>
<tr>
<td>AVP (pg/mL)</td>
<td>2.04</td>
<td>3.22*</td>
<td>3.87*</td>
</tr>
<tr>
<td></td>
<td>(1.82-3.58)</td>
<td>(2.77-6.16)</td>
<td>(2.93-10.92)</td>
</tr>
</tbody>
</table>

Effects of dobutamine and terlipressin on the level vasoactive hormones. Aldo, Aldosterone; ANG II, Angiotensin II; AVP, Arginine-vasopressin. *=p<0.05 and **=p<0.005 (Comparison between intervention periods and baseline); # = p<0.05 and ## = p<0.005 (Comparison between period 1 and period 2)
### TABLE 4: Types and numbers of adverse events

<table>
<thead>
<tr>
<th></th>
<th>Terlipressin N=20</th>
<th>Dobutamine N=10</th>
<th>Terlipressin + Dobutamine N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain/diarrhoea</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Urge to vomit</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Types and numbers of adverse event related to terlipressin, dobutamine and combined treatment.
Cirrhosis and ascites (N=245)

Not Eligible (N=218)
- Age>75 (N=9)
- HCC (N=19)
- TIPS (N=7)
- IHD/CHF (N=42)
- COPD (N=29)
- CKD (N=11)
- IDDM (N=25)
- Other* (N=57)
- Refused to participate (N=19)

Included and randomised (N=27)

Group A (N=11)
- Drop out (N=1)
  - urethral bleeding after placement of bladder catheter
  Group A (N=10)

Group B (N=11)
- Drop out (N=1)
  - alcoholic hepatitis during preparation period
  Group B (N=10)

Group C (N=5)
  Group C (N=5)
Relative effects of dobutamine and terlipressin

Group A
- Baseline
- Terli
- Terli + Dobu

Group B
- Baseline
- Dobu
- Terli

Group C
- Baseline
- Placebo
- Placebo

CO
MAP
1 SD

GFR
Renin
1 SD

Dobu
Terli
Placebo
Placebo

Downloaded from physiology.org/journal/ajpgi at Univ Southern Denmark-Syddansk Univ (130.226.087.010) on January 29, 2020.
Effects of terlipressin and dobutamine on heart rate

Group A

Group B

Group C

Heart rate
1 SD

Baseline Terli Terli + Dobu
Baseline Dobu Terli
Baseline Placebo Placebo
## Renal and Cardiovascular Effects of Dobutamine and Terlipressin in Cirrhosis and Ascites

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Cardiovascular Effects</th>
<th>Renal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dobutamine</strong></td>
<td>↑ CO</td>
<td>↔ GFR</td>
</tr>
<tr>
<td></td>
<td>↔ MAP</td>
<td>↔ C\textsubscript{Na}</td>
</tr>
<tr>
<td></td>
<td>↑ RAAS</td>
<td></td>
</tr>
<tr>
<td><strong>Terlipressin</strong></td>
<td>↓ CO</td>
<td>↑ GFR</td>
</tr>
<tr>
<td></td>
<td>↑ MAP</td>
<td>↑ C\textsubscript{Na}</td>
</tr>
<tr>
<td></td>
<td>↓ RAAS</td>
<td></td>
</tr>
<tr>
<td><strong>Terlipressin  + Dobutamine</strong></td>
<td>↑ CO</td>
<td>↔ GFR*</td>
</tr>
<tr>
<td></td>
<td>↔ MAP*</td>
<td>↔ C\textsubscript{Na}*</td>
</tr>
<tr>
<td></td>
<td>↑ RAAS</td>
<td></td>
</tr>
</tbody>
</table>

*compared with terlipressin as monotherapy