

Midodrine and albumin as a possible “winning pair” in managing paracentesis-induced circulatory dysfunction: a clinical case report

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Abstract. – BACKGROUND: Paracentesis-induced circulatory dysfunction (PICD) is a “silent killer syndrome” occurring after large volume paracenteses (LVPs). We here report an unusual case of PICD induced by right heart failure recognized and managed successfully.

CASE PRESENTATION: A 60-year-old woman was admitted to our Emergency Department for worsening dyspnea and hypoxia. Her medical history enclosed a chronic heart failure with reduced ejection fraction and post-stroke dysarthria associated to right hemiplegia. Clinical and laboratory examination defined a severe right-heart failure unresponsive to high-dose diuretic therapy. Diagnostic and therapeutic paracentesis was thus performed determining, initially, a progressive normalization of the abdominal volume, followed, subsequently, by a severe hypotension associated with an acute kidney injury (AKI) combined with severe hyponatremia associated with a normal cardiac output. In the hypothesis of a PICD, abdominal drainage and diuretic therapy were interrupted, reninemia sampling was performed, resulting in diagnostic, and treatment with albumin and norepinephrine was started. The latter was tapered and then replaced with Midodrine that conferred the possibility to reach clinical and laboratory stability, allowing relocation in a cardiological rehabilitation.

PICD represents an independent predictor of mortality. Midodrine’s prophylactic use in PICD has been suggested as a cheaper alternative to albumin, as it appears to improve renal perfusion and reduce ascites with better clinical handling, as demonstrated in our patient.

CONCLUSIONS: Our clinical case wants to show how not all PICDs are secondary to hepatic dysfunctions with Midodrine playing a possible therapeutic role by counteracting the pathophysiological mechanism in a rapid and non-invasive way, representing a valid therapeutic option in adjunction to albumin.

Key Words:

Midodrine, Paracentesis-induced circulatory dysfunction, Albumin, Ascites, Heart failure.

Introduction

Ascites can be divided into three grades, the last defined as “diuretic resistant” requiring large volume paracenteses (LVP)¹. It associates with remarkable neurohumoral activation of the sympathetic and renin-angiotensin-aldosterone system (RAAS) and very low urinary sodium excretion (<10 mEq/day) despite maximal tolerated doses of diuretics². Neurohumoral activation determines renal vasoconstriction and sodium reabsorption in the proximal tubule (mediated by norepinephrine and angiotensin II) and collecting tubules (aldosterone related)³. This explains why patients with diuretic resistant ascites should withdraw medications that decrease systemic blood pressure (and thus renal perfusion) such as beta blockers (BBs), angiotensin converting enzyme inhibitors, and angiotensin receptor II blockers to decrease the risk of developing a paracentesis-induced circulatory dysfunction (PICD). PICD is a “silent killer syndrome” occurring after LVPs giving clinical signs when complications are overt [e.g., hyponatremia, hepatorenal syndrome (HRS)]. Its onset correlates to increased mortality, thereby early identification is mandatory to ensure a successful treatment aiming at the restoration of an effective circulating volume (ECV). We here report an unusual case of PICD induced by right heart failure that was recognized successfully and managed with albumin and vasopressors (norepinephrine at first, and midodrine thereafter).

Case Presentation

A 60-year-old woman was admitted to our Emergency Department for worsening dyspnea, refractory lower limbs edema and ascites. Her medical history included chronic heart failure (NYHA class III) with reduced ejection fraction (EF 45%), good functioning mechanical mitral and aortic prostheses, bioprosthetic tricuspid valve regurgitation with moderate transvalvular leak (increased gradients: 11/7 mmHg) (Figure 1), secondary pulmonary artery hypertension (PAPs 65 mmHg) and permanent atrial fibrillation (AF) on vitamin K antagonist (VKA) and BB treatment (bisoprolol 2.5 mg twice daily). Her history also included post-stroke dysarthria associated with right hemiplegia, hypothyroidism, and multifactorial anemia.

On admission, she was hemodynamically stable [blood pressure (BP) 120/70 mmHg, heart rate (HR) 60 bpm], afebrile, eupneic at rest (SpO₂ 98% in ambient air) but easily fatigued at the minimal movement. Thoracic auscultation was positive for bilateral basal crackles and rales. Heart auscultation confirmed the presence of prosthetic valves characterized by a high pitched “clicky” sound with a central protosystolic murmur. Lower limbs were edematous (fovea sign) and symmetrical with overt ascites. Arterial blood gas (ABG) anal-

ysis in room air showed a slight rise in lactates (3 mmol/L) with PaO₂ 80 mmHg, PaCO₂ 32 mmHg, and pH 7.48. Electrocardiogram (ECG) confirmed an AF with a rapid ventricular response (110 bpm), right bundle branch block, and diffuse non-specific repolarization abnormalities. Blood tests revealed anemia (Hb 9.9 g/dl) with normal mean cell volume (MCV 88 fL), mean cell hemoglobin concentration (MCHC 33 g/dl), platelet and leukocyte count. An irrelevant increase in total and direct bilirubin values (2.05 mg/dl and 1.51 mg/dl respectively) was identified with normal serum creatinine values (1.1 mg/dl), and a slight increase in azotemia (85 mg/dl). Serum N-terminal brain natriuretic peptide (NT-proBNP) value was high (2.123 pg/ml). International normalized ratio (INR) was in its’ therapeutic range (2.6). Electrolytes, blood glucose, C-reactive protein (CRP), transaminases, and serum albumin were within the normal ranges (the latter being 4.3 g/dl). Ascites secondary to severe right-heart failure was thus defined and immediate therapy with high doses of intravenous (IV) diuretics (furosemide 250 mg, canrenone 200 mg) was initiated, with prior admission to our Emergency Medicine Unit.

Despite the high diuretic dosage, a small improvement in congestion was obtained. After 5 days of therapy, diagnostic and therapeutic para-

Bioprosthetic tricuspid valve regurgitation

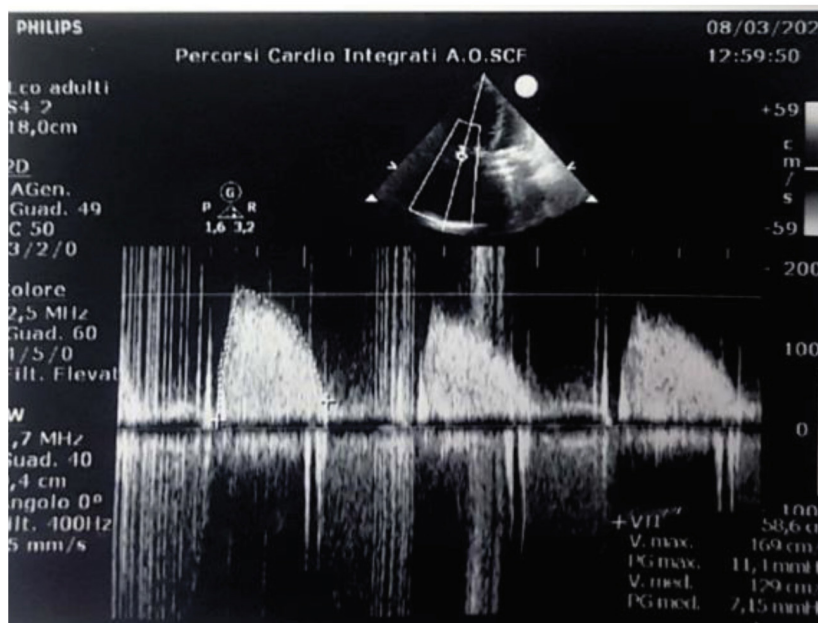


Figure 1. Moderate transvalvular leak (GP 11/7 mmHg).

centesis was performed, leaving a pig-tail-catheter for possible further drains. 2,500 ml of peritoneal effusion was removed bringing to recovery from the abdominal discomfort and perceived dyspnea. Analysis of the ascitic fluid was compatible with transudate [clear appearance, low cellularity, serum-ascites albumin gradient (SAAG) of 1.6 mg/dl]. The next four days were characterized by daily drainage of 1,500-2,000 ml of ascites followed by oncotic repletion with IV albumin infusion (10 grams per liter) with progressive normalization of the abdominal volume. However, the next day, the patient developed severe hypotension (BP 70/40 mmHg, HR 140 bpm), with dyspnea at rest (SpO₂ 91%) remaining afebrile. Blood tests showed no increase in leukocytes or CRP values, excluding a possible intercurrent infection, with blood cultures confirming sterility, despite the onset of an acute kidney injury (AKI) (creatinine 3.4 mg/dl, azotemia 118 mg/dl, K⁺ 5.7 mEq/l), combined to severe hyponatremia (Na⁺ 124 mEq/l) associated to a normal cardiac output (CO) identified at a point-of-care ultrasound (POCUS) evaluation.

On clinical suspicion of a PICD, abdominal drainage with diuretic treatment was stopped, reninemia sampling was performed, and treatment with IV hypertonic solutions (albumin supplementation of 1g/kg the first two days, followed by 30 g/day on the next two days) with vasopressor infusion (norepinephrine starting with 0.5 mg/h with an upward titration to 2 mg/h) were started. Elevated serum renin values confirmed diagnosis (616 ng/ml/hr, normal range 2.8-39.9). Given the anasarcat state, the infusion of diuretics was resumed gradually in a prudent manner, leading to progressive responsiveness (increased BP, urinary output, and creatinine normalization). Abdominal volume remained stable, with no evidence of further ascitic production during serial ultrasound scans. Noradrenalin was then tapered and withheld thanks to midodrine imbrication and replacement (reaching a balance with 10 mg orally three times daily) determining clinical and laboratory stability, allowing onward assignment to a cardiac rehabilitation ward.

Discussion

A “diuretic resistant” ascites requires LVP resulting in clinical improvement at the expense of a raised risk of developing complications including PICD in subjects unable to fully compensate systemic vasodilation. PICD is a marker of

effective hypovolemia resulting in an increase in plasma renin activity (PRA) after paracentesis^{4,5}. PICD was first described by Ginès et al⁶ in 1988. It brings to hyponatremia, development of HRS representing an independent predictor of mortality⁶. The pathophysiology is multifactorial and not completely understood. Decreased circulating volume and decreased systemic vascular resistance are implied, resulting in increased nitric oxide synthesis secondary to shear stress caused by reduced intrabdominal pressure and increased CO post-paracentesis⁷. Increased CO leads to a reflex mechanism of decreased systemic vascular resistance through a short-term downregulation of the sympathetic nervous system (SNS) and renin release secondary to cardiac volume receptor activation⁸. The resulting effective hypovolemia in turns leads to prolonged activation of the SNS and RAAS⁵. Therefore, patients that are unable to fully compensate for the systemic vasodilation are more likely to develop PICD with homeostatic effects lasting months⁹.

PICD is clinically a silent syndrome that is diagnosed by laboratory results with increases > 50% of baseline of PRA to > 4 ng/ml/h at six days after paracentesis¹⁰. Incidence is estimated to be 80% among patients not receiving any plasma volume expander, 38% in those receiving saline solution, and 20% in patients receiving albumin⁹. BBs may associate to PICD representing a risk factor for its development by worsening of hemodynamics, as demonstrated in our patient. Preliminary data¹¹ suggest that it is safe to abruptly discontinue BBs with no adverse effects on the hepatic venous pressure gradient bringing to a slight increase in the cardiac index¹¹. More to the point, BBs reduce survival by impairing cardiac function and secondary renal perfusion¹².

One of the simplest ways to prevent PICD is to limit the volume of fluid removal to 6 liters and throughout preventive approaches that include plasma volume expanders post-paracentesis (especially albumin) and vasoconstrictors (midodrine, terlipressin, and norepinephrine)¹³. In a quoted study⁶, 105 patients undergoing LVP were randomly assigned to receive albumin solution (10 g/L of ascites removed) or no albumin. Patients not receiving albumin were more likely to show signs of hemodynamic deterioration including an increase in PRA; these were also more likely to develop AKI and severe hyponatremia (21% versus 4% in those receiving albumin)⁶. Albumin, saline, dextran 70, and polygeline have all been used though albumin has been shown to be

superior¹⁴. This because albumin is an essential plasma protein with a 21-day half-life produced by hepatocytes accounting for 75% of plasma colloid oncotic pressure, detoxifies harmful reactive oxygen species, stabilizes the endothelium, prevents platelet aggregation, and modulates inflammatory responses¹⁵. Albumin infusion, therefore, may serve in ascites for a dual purpose: replenish the levels of circulating albumin and for the functional activity of the albumin pool. The need for colloid replacement to prevent effective hypovolemia after LVP remains controversial: likely not necessary for paracenteses of 5 liters or less while required for larger ones. The optimal dose has not been well studied: the only dose finding study¹⁶ comparing 4 g/L of fluid removed with 8 g/L found no difference in PRA or renal function at six days with no survival difference. The European Association for the Study of Liver Disease guidelines state that it is reasonable to give 8 grams of albumin per liter of ascites removed when more than 5 liters are removed¹⁷.

Among vasoconstrictors, frequently used in combination with albumin, terlipressin, norepinephrine, and midodrine have been applied. Terlipressin, a vasopressin 1 receptor agonist (starting with boluses from 0.5-1 mg every 4-6 hours to 2 mg every 4 hours and as a continuous intravenous infusion from 2 mg/day to 12 mg/day), increases systemic vascular resistance, reduces the portal pressure and has been used for several diseases including PICD for its efficacy in maintaining the arterial blood volume post paracentesis throughout splanchnic vasoconstriction¹⁸. Noradrenalin (potent alpha agonist) is an economical choice, valid in type I HRS [given intravenously as a continuous infusion 0.5 to 3 mg/h with the goal of raising the mean arterial pressure (MAP) by 10 mmHg], where its benefits in the PICD prevention are not well known¹⁹.

Midodrine (alpha agonist) acts on the alpha adrenergic receptors of the arteriolar and venous vasculature producing an increase in vascular tone and elevation of splanchnic blood pressure, circulating blood volume, and renal perfusion²⁰. It is effective starting with 5 mg orally three times daily every 24 hours (maximal dose 17.5 mg three times daily) to achieve a MAP >80 mmHg. Midodrine's prophylactic use in PICD has been suggested as beneficial and as a cheaper alternative to albumin¹³. Its addition can improve renal perfusion and reduce ascites²¹. In accordance with the above, in a trial²² with 40 patients undergoing LVP, patients were assigned to midodrine or albumin not detecting any difference in terms of PRA between the groups.

Our clinical case wants to show how, on one hand, not all PICDs are secondary to hepatic dysfunctions, but there is rather a problem of ECV as common trigger. In fact, our patient represents an infrequent case of PICD secondary to advanced heart failure: similar situations have been hardly mentioned by scientific evidence. On the other hand, we want to highlight the possible therapeutic role of midodrine, which, acting directly on peripheral vascular resistance, can counteract the pathophysiological mechanism responsible for PICD in a rapid, inexpensive and non-invasive way.

Conclusions

Current scientific and clinical evidence confirms how, volume expansion with albumin represents the mainstay, with vasoconstrictors representing a possible association. Furthermore, recent literature (including our reported case), want to emphasize how midodrine itself may represent an optional initial therapeutic partner or alternative to albumin in the medium to long term. This is also related to the fact that the bioavailability of the intravenous drug is comparable to the oral formulation, rendering clinical management easier.

Funding

None.

Conflicts of Interest

There are no conflicts of interest.

Informed Consent

Informed consent was obtained from the patient.

Authors' Contribution

Dr. Marigliano Benedetta: manuscript preparation; Dr. Internullo Mattia and Dr. Scuro Luigi: editing of manuscript; Dr. Marigliano Benedetta, Dr. Internullo Mattia, Dr. Tavanti Andrea, Dr. Del Vecchio Lucia Rita, Dr. Scuro Luigi, Dr. Colombo Giovanni Maria, Dr. Schito Maria Barbara, Dr. Guglielmelli Emanuele: data collection and patient management.

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