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Case Report

Worsening of proteinuria caused by combination therapy of hypertonic saline and low-dose furosemide for treatment of acute decompensated heart failure with overt diabetic nephropathy

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ABSTRACT

A combination of hypertonic saline and furosemide has been proposed as a new therapeutic approach for treating acute decompensated heart failure (ADHF). The advantages of this combination have not only been demonstrated in ADHF but also in refractory ascites due to liver cirrhosis. However, the therapeutic effects of this regimen have never been evaluated in ADHF with overt diabetic nephropathy (ODN). Here, we present an interesting case of a 35-year-old patient admitted to our hospital for ADHF with shortness of breath and systemic edema, complicated with hypertension, type 2 diabetes, and ODN. Echocardiography showed left ventricular enlargement and diffuse hypokinesis, with ejection fraction of 33%. Urinary findings showed total proteinuria of 3597 mg/day during the first day of hospitalization. We initiated decongestion therapy with continuous infusion of hypertonic saline and furosemide. In spite of increased diuresis, edema remained the same and serum albumin decreased from 2.7 g/dl to 2.0 g/dl, and proteinuria increased up to 7344 mg/day. The amount of proteinuria and serum albumin level gradually recovered over time after cessation of the therapy. These data suggest that the combination therapy worsens glomerular hypertension and ODN. Therefore, hypertonic saline and furosemide combination therapy should not be recommended for patients with ODN.

<**Learning objective:** Hypertonic saline and low-dose furosemide combination therapy has been proposed as a treatment option for ADHF, especially in refractory congestive heart failure cases. Nevertheless, the efficacy of this treatment in ADHF cases complicated with overt proteinuria is not fully elucidated. This therapy may induce increment of proteinuria in these patients due to aggravation of glomerular hypertension, and may be ineffective for decongestion or to treat edema.>

Introduction

Hypertonic saline and furosemide combination therapy has been reported as an effective treatment for acute decompensated heart failure (ADHF). This therapy was used mostly in cases of diuretic resistance, or in cases of refractory heart failure [1]. This therapy is also thought to be renoprotective since it preserved renal filtration function, as assessed by a significantly smaller increase in serum creatinine levels during the hospital stay of patients who were administered the combination therapy compared to patients given furosemide alone [2].

Type 2 diabetes mellitus (T2DM) is commonly seen in heart failure patients, who over a period of time develop overt diabetic nephropathy (ODN) due to long-standing diabetes mellitus (DM), complicated with hypertension, loss of renal function, peripheral edema, overt proteinuria, and hypoalbuminemia. However, the efficacy of combined therapy of hypertonic saline and furosemide in ADHF patients with associated ODN has never been validated.

This is a report showing a case of ADHF with associated ODN, in which administration of hypertonic saline and low-dose

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furosemide combination therapy led to worsening of the preexisting nephritic state.

Case report

A 35-year-old male patient was referred to the cardiology department of Hyogo College of Medicine due to dyspnea on exertion for the previous month and systemic edema for the past year. His body weight increased by 8 kg in the past 4 weeks. His blood pressure was recorded as 130/90 mmHg, and heart rate was 99 heartbeats/min. Clinical examination showed rales over the lower third of both lungs, raised jugular venous pressure, and edema in both lower limb extremities. On cardiac auscultation, a 3rd heart sound was heard. He was diagnosed as having ADHF and was admitted to our department for the treatment of ADHF in November 2012. He had been previously diagnosed with T2DM, hypertension, ODN (Stage 3, overt nephropathy) [3], and proliferative diabetic retinopathy, for which he had undergone laser treatment twice before. On admission, his serum sodium was 144 mEq/L, serum albumin was 2.7 g/dl, serum creatinine was 1.64 mg/dl, and plasma B-type natriuretic peptide was 612 pg/ml. Urinary finding showed total proteinuria of 3597 mg/day. A urine protein to creatinine ratio, which was obtained 2 days prior to admission in the outpatient department, was 8.045. Electrocardiogram showed regular sinus rhythm with complete right bundle branch block, and P sinistrocardiale. Chest X-ray showed bilateral pulmonary congestion with moderate pleural effusion. Transthoracic echocardiography showed enlargement of the left ventricle (LV), diffuse hypokinesis of LV, and distension of inferior vena cava (LV end diastolic diameter, 60 mm; ejection fraction, 33%; diameter of inferior vena cava, 25 mm without respiratory change). He was already on oral medication, which included a diuretic (furosemide 20 mg/day), an angiotensin II receptor blocker (candesartan 8 mg/day), and an angiotensin-converting enzyme inhibitor (lisinopril 10 mg/day).

Continuous intravenous infusion of hypertonic saline (1.7% solution of NaCl, 500 ml/day) in addition to 40 mg of furosemide was initiated. Although the treatment increased diuresis and slightly reduced body weight, neither his edema nor pleural effusion improved. In order to decrease edema, the dose of furosemide was increased up to 120 mg/day, but diuresis and body weight remained the same. As we continued hypertonic saline and furosemide combination therapy, the amount of proteinuria increased from 3597 mg/day to 7344 mg/day, and serum albumin level decreased from 2.7 g/dl to 2.0 g/dl (Table 1). We assumed hypoalbuminemia was worsened by hypertonic saline and furosemide combination therapy, via aggravation of glomerular hypertension. After cessation of the combination therapy, the amount of proteinuria decreased to 4480 mg/day and serum albumin level gradually recovered from 2.0 mg/dl to 2.4 mg/dl (Fig. 1). To increase diuresis and reduce edema, the patient was prescribed tolvaptan, a vasopressin type 2 receptor antagonist at 7.5 mg/day, and then the dose was increased up to 15 mg/day, and a thiazide diuretic (trichlormethiazide 2 mg/day) was added. But sufficient urinary volume could not be obtained and body weight slightly increased.

Discussion

We have previously reported the efficacy of intravenous salt supplementation with low-dose furosemide for treatment of ADHF [4]. However, the therapy did not decrease edema or reduce body weight in the ADHF patients complicated with ODN. On the contrary, it increased proteinuria, and lowered serum albumin level. This deterioration could be due to sodium loading that could have increased the intraglomerular pressure, which is already increased with hyperfiltration in patients with ODN, leading to aggravation of proteinuria and renal injury, rather than resolving edema.

In early stages of diabetic nephropathy, primary renal vasodilatation with a greater reduction in afferent relative to efferent arteriolar resistance results in increased intraglomerular pressure and glomerular hyperfiltration. This induces segmental glomerulosclerosis and causes nephron loss. At the same time, glomerulosclerosis induces hyperfiltration in the spared nephrons as a compensatory response to nephron loss, in an attempt to maintain glomerular filtration rate (GFR), further adding to the glomerular injury. In diabetic animal model, there is a correlation between urine albumin excretion and intraglomerular pressure, and therefore, intraglomerular hypertension in DM increases protein leakage across glomerular capillaries [5].

Sodium loading increases renal plasma flow (RPF) and GFR in mild heart failure patients [6]. GFR is determined mainly by filtration pressure and filtration coefficient. Therefore, sodium loading may increase intraglomerular pressure and proteinuria as a result of intraglomerular hypertension. In this patient, sodium loading may have directly worsened intraglomerular hypertension and aggravated glomerular injury, both leading to increase in proteinuria. Hyperfiltration caused by intraglomerular hypertension generally increases GFR and the amount of protein in urine. In this patient, however, hypertonic saline with furosemide therapy also increased serum creatinine level concurrently with the amount of protein in urine. Therefore, sodium loading may have other effects on renal function, in addition to causing intraglomerular hypertension. In spontaneously hypertensive rats, dietary salt loading demonstrated decreased RPF, increased renal vascular resistance and serum creatinine concentration, and increased proteinuria [7]. Increased proteinuria itself causes tubular injury through multiple pathways. Tubular injury has a link with reduction of RPF through increasing renal vascular resistance, consequently increasing serum creatinine concentration (Fig. 2) [8,9].

Table 1 Time course of blood examination and urinary findings.

Hospital day	−2	0	3	7	10	14	19	21	24
Serum albumin (g/ml)	2.7	2.7		2.3	2.0	2.0	2.4		2.4
BUN (mg/dl)	37	37	37	34	34	40	34	35	35
Cre (g/dl)	1.83	1.64	1.64	1.77	1.80	1.89	1.74	1.85	1.80
Ccr			22.1	41.5	40.6	25.5	19.3	49.4	20.3
Serum sodium (mEq/L)	142	144	143	144	144		142	141	141
24 h-Up (mg/day)		3597		7344	6027		4408		
Up/Ucr	8.045			5.835	5.571		5.321		
AST/ALT	27/21	21/16	17/14		10/11				17/13
Hematocrit	37.5	36.2	35	28.4	31.4	31.4	34.2	35.3	34.8
CRP	0.4		0.2	1.9	1.2	0.6		0.1	0.1

Abbreviations: BUN, serum blood urea nitrogen level; Cre, serum creatinine level; Ccr, creatinine clearance; 24 h-Up, 24 hour-urinary protein excretion; Up/Ucr, urine protein to creatinine ratios.