Successful Treatment of Acute Kidney Injury in Patients with Idiopathic Nephrotic Syndrome Using Human Atrial Natriuretic Peptide

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Abstract

The acute onset of idiopathic nephrotic syndrome (NS) is often accompanied by acute kidney injury, which can lead to congestive heart failure and lung edema. In this report, we present two cases of NS-induced acute kidney injury successfully treated with a low dose of carperitide, a human atrial natriuretic peptide. In combination with standard diuretic therapy and immunotherapy, carperitide retained the renal function and spared the need for renal replacement therapy, including hemodialysis. Although further investigation in clinical trials is required to validate these findings, carperitide may be useful for maintaining the renal function in cases of NS-induced acute kidney injury.

Key words: acute kidney injury, nephrotic syndrome, human atrial natriuretic peptide

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Introduction

Nephrotic syndrome (NS) is a disorder characterized by heavy proteinuria, hypoalbuminemia with systemic edema and hypercholesterolemia. Particularly in adults, idiopathic NS is often complicated by oliguric acute kidney injury (AKI), leading to congestive heart failure and pulmonary edema. The incidence of AKI is higher in older men (-60 years of age) and patients with hypoalbuminemia (1). Treatments for NS include immunotherapy (e.g., steroids and immunosuppressants), with the goal of reducing proteinuria, and diuretics, to address fluid retention. However, the pharmacological treatment of AKI complicated with idiopathic NS has not been established, and temporal renal replacement therapy (RRT) is often required to prevent life-threatening conditions due to excessive fluid.

Atrial natriuretic peptide (ANP) is a potent vasodilating hormone synthesized by the cardiac atria. Synthetic human ANP (hANP) is used as a therapeutic agent in cases of acute decompensated heart failure. Additionally, recent studies suggest that hANP may help to preserve the renal function in the cardiovascular surgical setting (2) and patients with contrast-induced nephropathy (3). The present report describes two cases of successful treatment of NS-induced AKI in which the continuous infusion of low-dose carperitide, a synthetic hANP, alleviated lung edema-related hypoxia and prevented acutely progressive renal failure, thereby preventing the need for RRT.

Case Reports

Case 1

An 84-year-old man was referred to our institution for the management of NS. He had developed leg edema two months and pleural effusion one month prior to admission. On admission, he complained of shortness of breath. Excessive fluid retention was diagnosed based on the presence of leg edema and lung congestion on a chest X-ray. The administration of 3 L/min of oxygen was required to maintain a pulse oximetry reading of 95%. The patient’s medical history was notable for hypertension; however, the baseline values of the renal function were unknown. The patient’s blood
pressure was 148/80 mmHg, his heart rate was 82 bpm and his axillary temperature was 36.5°C. The laboratory findings were as follows: serum albumin, 2.1 g/dL; total serum protein, 4.7 g/dL; serum creatinine, 1.87 mg/dL; total cholesterol, 250 mg/dL; C-reactive protein, 0.38 mg/dL; white blood cell (WBC) count, 9,500/μL; hemoglobin (Hb), 11.5 g/dL; and platelets, 17.0×10^4/μL. The levels of complement C3 and C4 were normal. The level of serum brain natriuretic peptide (BNP) was 53.6 pg/mL. Significant findings on a urinalysis included a urinary protein/creatinine ratio of 9.1 mg/g and hematuria with uniform red blood cells and hyaline casts. The selectivity index of urinary protein was 14.5%. The ejection fraction (EF) on a transthoracic echocardiogram (TTE) was 76% without wall motion abnormalities. The inferior vena cava (IVC) collapsed during inspiration.

The subacute onset of massive proteinuria with a low-to-moderate selectivity index and inactive urine sediment indicated minimal change nephrotic syndrome. There were no indications of underlying infectious disease or malignancy. A renal biopsy was not performed due to respiratory failure. Excessive whole body fluid was apparent on the physical findings and impaired oxygenation due to lung congestion was evident, which required the immediate initiation of diuretic therapy. As the patient’s systolic blood pressure was maintained as high as 130 mmHg, we then decided to start diuretic therapy, paying particular attention to the blood pressure. With the patient’s consent, therapy was initiated with furosemide and carperitide (0.0125 μg/kg/min) on hospital day 1 and oral prednisolone (45 mg/day, 0.75 mg/kg body weight on baseline) on hospital day 2. Despite increasing the dose of diuretics, the patient’s weight gain remained unchanged, and the serum creatinine level rapidly increased to 3.52 mg/dL (Figure A). The infusion of 12.5 g of albumin was provided to support the renal blood flow, and the dose of carperitide was increased to 0.025 μg/kg/min on hospital day 4. The hourly urine volume then abruptly increased, and the serum creatinine level and body weight began to decrease beginning on day 6. The patient’s systolic blood pressure remained over 120 mmHg, and no symptoms indicating hypotension were observed during the diuretic therapy. On day 81, he was discharged with complete remission of NS. The serum creatinine level had improved to 1.14 mg/dL. No RRT or immunotherapy, other than prednisolone, were utilized during this period.

Case 2

A 61-year-old woman was referred to our institution for the management of AKI following NS. She had experienced the onset of leg edema three months previously and been admitted to another institution for the management of edema one week before admission to our hospital. She was diagnosed with NS and received daily infusions of furosemide and albumin; however, oliguria gradually developed, and the serum creatinine level increased from 0.74 mg/dL to 1.8 mg/dL.

On admission to our institution, the patient was noted to have leg edema and recent weight gain, although she denied shortness of breath and orthostatic dizziness. On a physical examination, her body weight was 59.1 kg (-7 kg higher than the baseline). Her vital signs were as follows: blood pressure, 132/78 mmHg; heart rate, 70 bpm; pulse oximetry on room air, 94%; and axillary temperature, 36.6°C. Significant physical findings included coarse crackles and decreased vocal fremitus in the left lung field, as well as pitting leg edema.

The laboratory findings were as follows: serum albumin, 1.5 g/dL; total serum protein, 4.0 g/dL; blood urea nitrogen, 37.3 mg/dL; serum creatinine, 2.41 mg/dL; total cholesterol, 480 mg/dL; C-reactive protein, 0.04 mg/dL; WBC count, 4,700/μL; Hb, 14.7 g/dL; and platelets, 26.9×10^4/μL. The levels of complement C3 and C4 were normal. The level of urinary protein excretion was 10.0 g in 24 hours. The selectivity index of urinary protein was 15.6%. The EF on TTE was 67% without wall motion abnormalities, and the IVC diameter was 12.7/18.1 mm.

In terms of the etiology of NS, no indications for infectious diseases or underlying systemic disease (e.g., diabetes, lupus, cancer) were observed. A needle biopsy of the kidney was performed on hospital day 1, and a daily infusion of prednisolone (60 mg, 1 mg/kg body weight on baseline) was initiated on hospital day 2 based on the diagnosis of minimal change nephrotic syndrome. The findings of the renal biopsy, including podocyte foot process effacement, supported a diagnosis of minimal change nephrotic syndrome but did not indicate acute tubular necrosis or interstitial edema.

As a result, high-dose furosemide was continued to treat the systemic edema on hospital day 1 (Figure B). However, the patient’s urine volume gradually decreased to 10 mL/h, and the serum creatinine level increased to 3.40 mg/dL on day 3. Since high-dose furosemide had already been used, the continuous infusion of carperitide was initiated in an effort to avoid RRT.

On day 4, the urine volume was markedly increased, and the patient’s body weight began to decrease in association with a gradual improvement in the serum creatinine level. However, upon cessation of the carperitide infusion on hospital day 6, the serum creatinine level transiently increased then decreased again, likely because the steroids began to work effectively on the NS without carperitide. A low systolic blood pressure below 110 mmHg was not observed during the administration of carperitide. The patient continued therapy, including steroids and diuretics, for NS after being transferred to the other institution on day 11, and remission of NS without re-exacerbation of AKI was reported one month later.

Discussion

A recent retrospective study (1) showed that AKI, defined according to the newly developed RIFLE international consensus classification criteria (4), was observed in 95 of 277
Figure. Clinical course of Case 1 (A) and Case 2 (B). Medications are indicated on the top of the panel. Serum creatinine and body weight are indicated in the middle of the panel. The urine volume and urinary protein excretion for 24 hours are indicated at the bottom of the panel. Conversion factor for units: serum creatinine in mg/dL to mol/L, ×88.4.
adult idiopathic NS cases, consistent with the observations of previous studies. Immunotherapy takes some weeks to reduce proteinuria and increase the glomerular filtration rate (GFR), thereby alleviating fluid excess and hypoxia. Therefore, nephrologists must consider strategies to support the renal function in patients with NS-induced AKI until immunotherapy becomes effective. Because hemodialysis/ultrafiltration is associated with significant risks, especially in elderly patients, developing an alternative to RRT would be of benefit for such patients. The etiology of NS-induced AKI comprises hypovolemia, excessive diuretics, renal vein thrombosis (5) and acute tubular necrosis (6); however, the major hypotheses include reduced “glomerular permeability” and “glomerular hypoperfusion” (7). Synthetic natriuretic peptides improve the GFR by modulating glomerular permeability (8) and arteriole resistance (9), elevating the renal blood flow and relaxing mesangial cells (10). Recent reports suggest that synthetic natriuretic peptides inhibit the reabsorption of sodium and water in distal nephrons in humans (11) and may alleviate the dysfunctional ANP signaling observed in the renal tubules of animals with NS (12).

Interestingly, in case 1, the fact that the urine volume increased one hour after the infusion of albumin and carperitide suggests that carperitide requires intravascular volume to increase the GFR and achieve diuresis. Worsening of proteinuria is expected when glomerular hypoperfusion improves. In case 1, the decrease in proteinuria observed starting on day 1 indicated that the corticosteroid therapy had become effective, contributing to the improvement of glomerular hypoperfusion, although fluid excess was a critical clinical manifestation at that point. The transient worsening of proteinuria may have been masked by the 24-hour urine collection. However, the rapid and remarkable increase in the urine volume within one hour after the infusion of albumin in the presence of carperitide observed at the bedside supports our hypothesis that carperitide requires intravascular volume to achieve diuresis.

In case 2, a decrease in the urine volume and re-elevation of the creatinine level were observed following the cessation of the carperitide infusion, suggesting that the renal protective effects of our therapeutic approach were dependent on hANP rather than steroids. Using a low dose of natriuretic peptide may help to prevent any associated adverse effects, including hypotension (8, 11), as evidenced in the present cases. According to previous reports (7-9, 11), low-dose hANP therapy can improve the glomerular filtration fraction and inhibit tubular reabsorption of sodium, although it does not reduce systemic arterial resistance. This favorable orchestration may have contributed to the treatment of AKI in the present cases.

Despite the outcomes of the present cases, the Kidney Disease Improving Global Outcome (KDIGO) clinical guidelines for AKI (13) suggest that hANP is not an effective therapy for preventing or treating AKI, as it is controversial whether high-dose hANP improves the clinical outcomes of AKI patients (14-16). As stated in the KDIGO guidelines (13), highly qualified clinical trials using lower doses of ANP, similar to those employed in the present cases, are needed to establish the efficacy of ANP in patients with AKI.

In conclusion, treatment with ANP appears to result in a temporary increase in GFR, while low-dose carperitide is useful for treating idiopathic NS-induced AKI.

The authors state that they have no Conflict of Interest (COI).

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References
