



Impact of high-dose diuretic combination therapy on volume status in peritoneal dialysis patients

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Volume overload is directly linked to cardiovascular disease (CVD), which is the leading cause of death in peritoneal dialysis (PD) patients, due to hypertension and congestive heart failure. Adequate volume control could be more important for improving PD patient survival than small solute clearance. PD allows less restricted fluid intake compared with hemodialysis (HD), which is advantageous because of continuous ultrafiltration (UF), although the actual frequency of volume overload in PD and HD is comparable [1]. PD is also known to preserve residual renal function better than HD; residual renal diuresis (RRD) is associated with improved patient survival [2]. However, residual urine volume does not necessarily indicate volume status because the latter could also be affected by other factors, such as fluid intake, and slight overhydration (OH) might help with RRD preservation [1]. A 1-year randomized controlled study (RCT) designed to evaluate the efficacy of high-dose loop diuretics (furosemide 250 mg/day) in 61 PD patients reported increased urine volume and improved fluid balance in the furosemide monotherapy group over the placebo group [3]. However, little is known about the efficacy of combination therapy with high-dose diuretics in PD patients.

In this issue of *Kidney Research and Clinical Practice*, Witoon et al [4] assessed the impact of high-dose diuretic combination therapy in patients on PD. Fifty-one prevalent PD patients were enrolled in the 6-month double-blinded RCT. The mean dialysis duration was 12 months, although this was still early in the course, and the mean baseline residual urine volume was 855 mL/day on furosemide (1,000 mg/day) therapy. All patients were treated with furosemide (1,000 mg); the study group received triple diuretic combination therapy (furosemide 1,000 mg/day, spironolactone 50 mg/day, and hydrochlorothiazide 100 mg/day), while the control group was given furosemide (1,000 mg/day) only. Medications were double-blinded for both the investigators and the patients by re-encapsulation. At 6 months from baseline, the change in urine volume was higher in the study group and found to be 312 mL/day and 120 mL/day in the study and control groups, respectively. The bioimpedance-measured OH status was also more favorable in the study group at 6 months, with a mean change in OH at 6 months of -0.48 L and $+1.49$ L in the study and control groups, respectively. Two patients on combination therapy were anuric at the start of the study (less than 100 mL/day). This study is important because it was the first double-blind RCT to demonstrate the effect of a high-dose diuretic combination in PD patients. Of the 51 patients enrolled, 4 were lost to follow-up, and 4 died during the study period, leaving 43 for data analysis, which did impact the strength of the evidence. The diuretics in this study were used at considerably higher dosages than those in earlier studies. The largest dose used in PD studies before this was furosemide at a dose of 250 mg/day [3]. In a study of pre-dialysis stage patients, the increases in all-cause and cardiovascular mortality over 3 years were greater in the

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high-dose furosemide (> 50 mg/day) group than in the low (1–25 mg/day) to moderate (26–50 mg/day) dose group [5]. While the cause for the increased mortality remains unclear, furosemide-induced sympathetic activation has been proposed as a mechanism. In this study, however, despite the much higher dosage (20 times at least) of furosemide (1,000 mg/day) and treatment duration of 7 months (run-in period included), there was no report of side effects. The high dose of 1,000 mg/day of furosemide is not usually prescribed in clinical practice even in patients with end-stage renal disease, although a high-dose furosemide tablet (500 mg/tablet) is available (Lasix Special[®], Hoechst Ltd., Canada; Diuresal 500 mg Tablet[®], Ennogen Pharma Ltd., UK) in several countries, including countries in Europe and Canada. Based on information for the user, a maximum dose of 1,000 mg or 2,000 mg/day can be prescribed in patients with severely impaired renal function. Therefore, a high or mega-dose of furosemide might be possible, and some clinicians are currently prescribing the mega-dose of furosemide. The use of mineralocorticoid receptor antagonists can provide several advantages beyond diuresis in PD patients. According to the Chronic Renal Insufficiency Cohort Study results, in participants with chronic kidney disease, a higher aldosterone concentration was independently associated with congestive heart failure [6]. The administration of spironolactone 25 mg/day to PD patients was associated with an improved left ventricular mass index in a 2-year RCT [7]. The dosage of spironolactone in the present study was 50 mg/day. *In vitro*, spironolactone has been shown to block the epithelial-mesenchymal transition of human peritoneal mesothelial cells and, thus, prevent peritoneal fibrosis [8]. The risk of severe hyperkalemia has been relatively low in PD patients since potassium clearance is achieved by the peritoneal membrane. The hydrochlorothiazide (100 mg/day) used in this study was also at a high dosage. It is well-known that combination therapy of loop diuretics and thiazides has a synergistic diuresis effect in advanced renal failure patients. In the present study, volume status was evaluated with the bioimpedance-measured OH status. Bioimpedance allows easy and repetitive measurement of volume in PD patients, enabling early detection of volume overload and offering advantages for regular monitoring.

Adequate volume control is critical for improving survival in PD patients because this is a modifiable fac-

tor that can reduce the risk of CVD [1]. Four patients (2 switches to HD due to UF failure and 2 deaths due to CVD) were not included in the final data analysis of this study. Because UF failure and cardiovascular death are closely linked to volume overload, the exclusion of these cases from the analysis weakens the strength of the evidence and leaves room for further investigations.

Initiating dialysis in end-stage renal disease usually involves decreased diuretic efficacy. As such, diuretics are often discontinued in an attempt to reduce pill burden. However, in a recent study (EUROBCM study), more than 50% of PD patients had an OH status as assessed by bioimpedance, a rate comparable to that observed in HD [9]. Congestive heart failure is common in PD patients, based on a report from Hong Kong, and the prevalence of *de novo* and recurrent heart failure in PD patients is 28% and 62%, respectively [10]. If peritoneal UF fails to sufficiently correct the volume overload, high-dose combination diuretics should be considered. In conclusion, although the results are promising, the 7-month study period was insufficient to completely assess the efficacy and side effects of the combination therapy; therefore, a larger and longer study is warranted. In addition, to better understand the patient perspective, a patient questionnaire regarding pill burden might also be needed.

Conflicts of interest

The author has no conflicts of interest to declare.

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