Int J Clin Exp Med 2017;10(2):3321-3328
www.ijcem.com /ISSN:1940-5901/IJCEM0045534

Original Article

Effect of diuretic and ultrafiltration on edema and renal residual function in peritoneal dialysis patients

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Received June 24, 2016; Accepted December 18, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Objectives: To compare the effect of diuretic and ultrafiltration on edema and residual function in peritoneal patients. Methods: Fifty-two peritoneal dialysis patients treated for more than 3 months in a single center were involved in this retrospective study. Those patients who suffered from mild or moderate edema and produced more than 400 ml of urine per day were divided into a diuretic group (26 cases) and a control group (26 cases). The diuretic group received oral furosemide 120 mg per day with original peritoneal dialysis prescription, and the control group received high glucose (2.5% or 4.25%) dialysate. Volume marks, biochemical index, sodium excretion, decline of glomerular filtration rate changes, and dialysis prescription were compared between the two groups after 6 months intervention. Results: After 6 months intervention, the proportions of edema in the two groups were all obviously improved ($P<0.01$) with significant weight loss ($P<0.05$) and satisfying blood pressure control ($P<0.05$). The patients in the diuretic group achieved higher urine volume ($P<0.01$), less dialysis ultrafiltration ($P<0.01$), and higher urine sodium excretion ($P<0.01$) than the patients in the control group. The decline speed of glomerular filtration rate (GFR) in the diuretic group was markedly slower than that in the control group ($P<0.05$). There were no significant differences in peritoneal dialysate sodium excretion, blood pressure, and in blood urea nitrogen, creatinine, albumin, and hemoglobin levels between the two groups after 6 months intervention. However, the blood glucose concentration was much higher in the control group than in the diuretic group ($P<0.05$), at least partly because of higher concentrations of dialysis fluid glucose ($P<0.05$). Conclusions: Furosemide may help protect residual renal function by reducing hypotensive episodes during dialysis with a lesser incidence of hypokalemia, hypoproteinemia, hypotension, and glucose metabolic disturbance than hyperosmotic dialysate.

Keywords: Diuretics, edema, peritoneal dialysis, renal function

Introduction

Fluid status and volume balance are extremely important in patients with chronic kidney disease (CKD) stage 5, as cardiovascular disease, including congestive heart failure and hypertension, is one of the leading causes of death in this patient group [1]. Peritoneal dialysis (PD) is an effective replacement therapy to control volume and blood pressure, particularly as renal removal provides a significant proportion of total solute and water clearance. A greater urine volume (UV) allows physicians greater opportunity for optimal control of fluid balance. Despite the theoretical advantages of PD over hemodialysis (HD) in patients with chronic cardiac disease, the clinical experiences reported in this risk group are controversial [2]. As residual renal function declines, inadequate water and solution removal results in a serious volume expansion in patients on long-term peritoneal dialysis. It is an important factor of high incidence of cardiovascular comorbidity that is also a serious risk factor for mortality in PD patients [3]. From the reanalysis of the CANUSA data, it became apparent that residual renal function (RRF) is one of the most powerful predictors of outcome in PD patients [4].

Unfortunately, RRF declines during treatment by PD, albeit at a lower rate than during treatment by classic HD. Longitudinal studies have shown that RRF progressively declines with time on dialysis. In general, most PD patients will have lost their RRF within 3-5 years after the start of their treatment [5]. In the CANUSA study [4], RRF decreased from 3.8 to 1.4 ml/min over a mean follow-up period of 2 years. Lameire et al [6] reported that in long-term PD patients, the contribution of RRF to overall

clearance decreased from 28% to 5% after 5 years. Sufficient urinary volume excretion not only allowed PD patients to maintain fluid balance, but also decreased the incidence of cardiovascular comorbidity. Ates [7] showed that the clinical outcome improved with higher volume removal and higher RRF, and decreased if the patient had hypertension, which was a sign of volume overload. Wang [8] demonstrated an inverse relationship between RRF and left ventricular hypertrophy, and between RRF and hypertension. Therefore, the protection of RRF from the start of dialysis is indispensable for the management of volume status and for a satisfying outcome in PD patients.

With the decline of residual renal function, significant UV decrease associated with undemanding dietary salt restriction resulted in volume expansion, which was an important and independent predictor of overall survival and cardiovascular death in the ADAMEX study [9]. Therefore, daily peritoneal ultrafiltration may offer to cardiorenal patients the beneficial result that nephrologists are longing to achieve with nocturnal HD or more frequent HD schedules [10]. Many clinical studies have demonstrated that improvement of fluid removal by dialysis ultrafiltration (UF) could slow the development of cardiovascular disease and minimize complications of existing cardiovascular disease and a dramatic reduction in hospitalization rates [11, 12]. Some experts reported that sodium removal was limited in peritoneal dialysis patients and mortality was correlated with fluid and sodium removal [13]. Hypertonic glucose dialysate is effective in inducing rapid removal of fluid, improvement of symptoms, high mass clearance of sodium, and good blood pressure control by increase dialysis ultrafiltration output [14]. In the European APD (automatic peritoneal dialysis) Outcome Study (EAPOS) [15], a fast decline of RRF occurred in patients who used long-term hypertonic glucose dialysate. However, as patients were anuric, volume regulation only attributable to peritoneal ultrafiltration whereas small solute clearance was adequacy or not [16]. Moreover, patients who used icodextrin dialysate had a faster decrease in their urinary output and RRF and an increase in dialysis ultrafiltration.

Furosemide, the most common loop diuretic, is used to enhance sodium and water removal, and is used among the prevalent dialysis patients in some dialysis centers [13]. Loop diuretics produce a significant reduction in blood pressure (BP) and a sustained volume balance in dialysis patients, which might increase their survival [17]. However, the role of loop diuretics in residual renal function protection is unclear. There was no effect from diuretics if the patient passed less than 100 ml of urine per day [18]. However, a prospective observational study showed that hemodialysis patients on diuretic therapy were twice more likely than patients not on diuretic therapy to retain RRF after 1 year. Medcalf [19] studied the use of furosemide in a prospective, randomized controlled trial over a 12-month period and showed that long-term administration of furosemide in pharmacological doses increases urine volume. Moreover, furosemide had no effect on preserving RRF. In contrast, some studies showed that diuretics use was associated with a rapid decline of RRF in patients on long-term peritoneal dialysis [5, 20].

Although many experts believe that diuretics are beneficial to PD patients with RRF [18], more clinical evidence is needed. It is clear that when heavy volume overload status occurs, as in congestive heart failure, increasing dialysis ultrafiltration is needed to improve the fluid balance and symptoms [8]. There is less clinical evidence in PD patients with RRF who suffer from mild or moderate fluid retention. Choosing between high glucose osmotic dialysate and diuretic as the appropriate therapeutic regimen is a challenge. The aims of this study were to confirm in peritoneal patients with mild or moderate versus high glucose osmotic dialysate the effect of furosemide on the decline of renal residual function, which is believed to serve as a new prognostic factor for all-cause mortality and death-censored technique [21].

Materials and methods

Study design

Peritoneal dialysis patients treated for more than 3 months in a single center were involved in this retrospective cohort case-control study. Those patients who suffered from mild or moderate edema and produced more than 400 ml of urine per day were randomly divided into a diuretic group and a control group. The ran-

Table 1. Demographic characteristics of the two group

	Diuretic	Control	Statistic	*P* value
Number	26	26		
Sex male/female	19/7	16/10	X^2=0.787	0.375
Median age	51.6±23.1	53.8±19.7		
Primary disease			X^2=1.064	0.786
Primary glomerular nephritis	21	18		
Diabetes mellitus	3	5		
Hypertension	1	2		
Interstitial nephritis	1	1		
Body weight (kg)	59.20±11.09	60.03±11.38	*t*=0.882	0.447
Urine volume (ml)	609.21±444.33	698.64±470.38	*t*=-0.981	0.375
Ultrafiltration (ml)	455.18±520.47	439.47±405.93	*t*=1.335	0.253
Total fluid output (ml)	1064.38±869.44	937.11±815.33	*t*=0.798	0.451
SBP (mmHg)	144.36±20.7	146.5±21.72	*t*=1.382	0.217
DBP (mmHg)	89.38±11.38	88.91±15.12	*t*=2.167	0.328
GFR (ml/min/m)	3.41±2.77	3.88±2.62	*t*=-0.721	0.512
Serum sodium (mmol/l)	139.07±5.45	142.21±4.31	*t*=0.274	0.253
24 h Urinary sodium excretion (mmol)	79.84±28.61	80.71±26.24	*t*=-1.14	0.337
24 h peritoneal dialysis sodium excretion (mmol)	864.97±91.30	849.46±89.64	*t*=0.025	0.732
Total glucose content of Dialysate per day (g/d)	106.05±61.91	103.24±47.74	*t*=0.163	0.523
Blood sugar (mmol/l)	4.56±1.52	4.49±1.35	*t*=-0.135	0.239
Serum urea nitrogen (mmol/l)	18.40±5.21	17.90±4.94	*t*=1.038	0.537
Serum creatinine (umol/l)	709.03±202.33	674.32±218.97	*t*=-0.461	0.332
Serum albumin (g/l)	31.67±4.18	32.9±93.98	*t*=0.546	0.457

domisation schedule was generated off site with a pseudo-random number generator in SAS version 6 (SAS Institute, Cary, NC). Collect relevant clinical indicators and compared statistically. All the study was approved by the Ethical Committee.

Patients and sample size

Peritoneal dialysis outpatients followed by the peritoneal dialysis center of the first affiliated hospital of Xi'an Jiaotong University from January 2012 to January 2014 were included in this cohort case control study. All the clinical data were obtained from the patient's clinical recording. The patients who fulfilled the following criteria were included: (1) peritoneal dialysis for more than 6 months at the onset of the study; (2) followed-up regularly in the center; (3) suffering from mild edema (only ankle) or moderate edema (below knee); (4) urine volume was above 400 ml per day; (5) treated by diuretic or hyperosmotic dialysate for at least 6 months. Exclusion criteria included any of the following: (1) serious edema (whole body or accompanied with acute left heart failure or pulmonary edema); (2) urine volume lower than 400 ml per day. The dialysate used in this study was produced by American Baxter international company. All patients received the same health education by the same team and had no objection to proprietary rights of clinical data. Before the start of the trial, we estimated that we needed a sample of Twenty eligible patients per group by a two tailed test. And then we increased the sample size to Twenty-six pregnant women per group to account for some data loss.

Treatment procedures

Fifty-two patients were randomly divided into two groups. Twenty-six patients were in the diuretic group, and twenty-six patients were in the control group. The diuretic group received the original peritoneal dialysis prescriptions (oral furosemide 120 mg per day (40 mg t.i.d)), whereas the control group received high glucose (2.5% or 4.25%) dialysis fluid. The observation period lasted for 6 months. All patients used the dialysate produced by America Baxter Company.

Table 2. Comparison of biochemistry and volume status markers in the two groups before and after intervention for six months

	Diuretic group		CIAD		Control group		CIAC		CDCI	
	Intitial	After intervention	t	p	Intitial	After intervention	t	p	t	P
Body weight (kg)	59.20±11.09	56.36±12.72	-3.417	0.025	60.03±11.38	55.40±12.26	-3.320	0.033	-0.741	0.462
ΔBody weight (kg)	--	5.13±1.03	--		--	5.69±3.24	--		1.142	0.285
Urine volume (ml)	609.21±444.33	965.55±470.39	-2.721	0.008	698.64±470.38	569.62±474.13	0.494	0.277	-2.298	0.025
Ultrafiltration (ml)	455.18±520.47	425.00±283.31	0.494	0.575	439.47±405.93	708.64±338.23	2.611	0.011	2.249	0.021
Total fluid output (ml)	1064.38±869.44	1201.56±753.61	2.534	0.014	937.11±815.33	1278.26±712.36	2.349	0.022	0.388	0.700
SBP (mmHg)	144.36±20.7	138.08±23.37	-2.638	0.022	146.5±21.72	136.04±22.51	2.019	0.037	-0.402	0.689
DBP (mmHg)	89.38±11.38	80.04±11.94	-1.034	0.300	88.91±15.12	80.25±12.62	0.644	0.523	0.464	0.645
ΔGFR (ml/min/m)	--	0.09±0.16	--		--	0.19±0.36	--		2.278	0.029
GFR (ml/min/m)	3.41±2.77	2.99±2.20	-1.023	0.448	3.88±2.62	2.17±1.97	-1.140	0.377	1.274	0.208
Serum sodium (mmol/l)	139.07±5.45	134.42±27.27	1.401	0.166	142.21±4.31	140.51±31.23	0.523	0.603	1.143	0.258
24 h Urinary sodium excretion (mmol)	79.84±28.61	91.40±30.63	2.877	0.005	80.71±26.24	77.16±20.99	1.285	0.243	2.283	0.026
24 h peritoneal dialysis sodium excretion (mmol)	864.97±91.30	850.25±81.77	-0.063	0.950	849.46±89.64	1122.32±93.44	-2.338	0.018	3.375	0.013
Total glucose content of Dialysate per day (g/d)	106.05±61.91	99.23±14.03	0.854	0.396	103.24±47.74	144.66±45.36	-2.329	0.023	-2.697	0.009
Blood sugar (mmol/l)	4.56±1.52	4.68±1.98	0.339	0.736	4.49±1.35	7.72±4.05	-2.053	0.047	-2.298	0.029
Serum urea nitrogen (mmol/l)	18.40±5.21	19.81±4.45	0.554	0.581	17.90±4.94	20.57±3.26	-1.577	0.052	-0.666	0.508
Serum creatinine (umol/l)	709.03±202.33	794.53±256.94	1.110	0.272	674.32±218.97	820.72±226.16	-2.534	0.014	0.554	0.581
Serum albumin (g/l)	31.67±4.18	35.42±4.29	-2.053	0.044	32.9±93.98	36.62±4.12	-2.217	0.031	-1.063	0.293

CIAD: Comparison between Intitial and After intervention in Diuretic group; CIAC: Comparison between Intitial and After intervention in Control group; CDCI: Comparison between Diuretic group and Control group after 6 month Intervention. ΔBody weight: change value of Body weight; ΔGFR: change value of GFR/6.

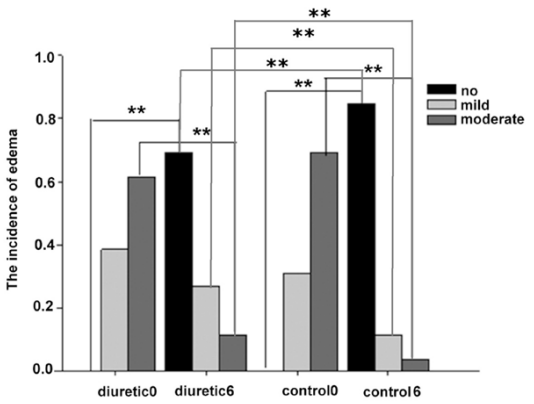

Figure 1. Change in edema status after intervention with different therapies. There is a significant (P<0.001) increase in the percentage of no edema up to 69.2% (diuretic group) and 84.6% (control group). The incidence of moderate edema dropped from 61.5% to 11.5% in the diuretic group (P<0.01) and from 69.2% to 3.8% in the control group (P<0.01) after six months of intervention. The incidence of no, mild and moderate edema was significantly different between the diuretic and control group after six months of intervention. ***P*<0.01.

Main outcome measure

The main outcome measures included volume status markers, such as incidence of edema, change in body weight, blood pressure, serum sodium, sodium excretion in urine, urine volume, volume of ultrafiltration; biochemical markers, such as hemoglobin, serum albumin, blood urea nitrogen, creatinine level and total glucose content of dialysis fluid and decline of glomerular filtration rate (GFR). Those markers were calculated at the beginning of the intervention and 6 months after the beginning of intervention. The proportion of hypokalemia, hypoproteinemia, hypotension, and glucose metabolic disturbance were investigated 6 months after the beginning of the intervention.

GFR was calculated as the BUN-to-creatinine ratio. The average decline rate of GFR every month (ΔGFR) was calculated by subtracting the GFR at the start point from that at 6 months, then dividing by 6 [$\Delta GFR=(GFR_6-GFR_0)/6$)].

The change of volume state, the advert incidence, and ΔGFR were compared between the two groups at the end of the observation period.

Statistical analysis

We performed all statistical analyses using the Statistical Package for Social Science (SPSS) version 16.0 for Microsoft Windows (SPSS Inc. Chicago, IL, USA). All data are presented as mean ± standard deviation. Independent samples paired-t test was used to analyze the differences between the groups. Chisquare test or Fisher exact probability method was used to compare enumeration data. And statistical significance was accepted for P<0.05.

Results

Demographic characteristics

All patients were divided into a diuretic group (26 cases) and a control group (26 cases). At the beginning of the study, the demographic characteristics of the two groups are summarized in **Table 1**. No significant differences were observed in clinical parameters such as sex characteristic, age, primary diseases, edema status, body weight, GFR, blood pressure, urine volume, serum sodium, urinary sodium excretion, and so on.

Comparison of edema status

After 6 months of intervention, all the patients in the two groups achieved a significant improvement in volume status (P<0.05), with no significant difference in weight loss (P>0.05), and a significant (P<0.001) increase in the percentage of no edema up to 69.2% (diuretic group) and 84.6% (control group). The incidence of moderate edema dropped from 61.5% to 11.5% in the diuretic group (P<0.01) and from 69.2% to 3.8% in the control group (P<0.01) after six months of intervention. The incidence of no, mild and moderate edema was significantly different between the diuretic and control group after six months of intervention (**Table 2**; **Figure 1**).

Comparison of biochemistry

The uv in the diuretic group was significantly higher at 6th months than Intitial (P<0.01). The uf in the control group was significantly higher at 6th months than Intitial (P<0.01). At 6th months, the uv in the diuretic group was significantly higher than that in the control group (P<0.05), and the uf is significantly lower than that in the control group (P<0.05) (**Table 2**; **Figure 2**). The systolic pressure was significantly decreased (P<0.05) in both groups. Furthermore, the sodium excretion in the urine

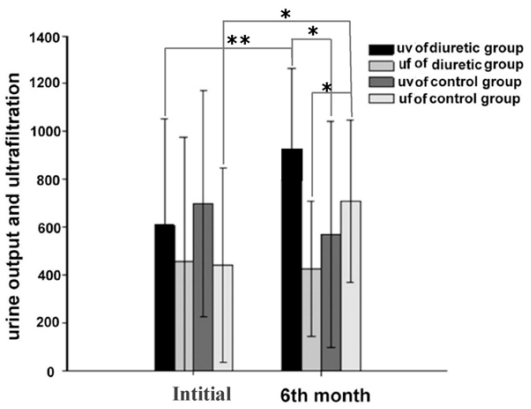

Figure 2. Comparison of urine output and dialysis ultrafiltration before and after intervention in two groups. The uv in the diuretic group was significantly higher at 6th months than Intitial (P<0.01). The uf in the control group was significantly higher at 6th months than Intitial (P<0.01). At 6th months, the uv in the diuretic group was significantly higher than that in the control group (P<0.05), and the uf is significantly lower than that in the control group (P<0.05). uv: Urine volume; uf: Ultrafiltration; *P<0.05; **P<0.01.

was higher in the diuretic group than it was in the control group (P<0.01). Although there was no significant decline in GFR in both groups after 6 months, the average decline rate of GFR every month in the diuretic group (0.09±0.16 ml/min/m) was markedly slower than that in the control group (0.19±0.36 ml/min/m) (P<0.05) (**Table 2**). There were no significant differences in blood pressure, blood urea nitrogen, creatinine, albumin, and hemoglobin levels between the two groups at the end of the observation period. However, sodium excretion from peritoneal dialysate was higher in the control group than in the diuretic group (P<0.01), while sodium excretion from urine output was higher in the diuretic group than in the control group (P<0.01). In addition, blood glucose concentration was significantly (P<0.01) increased in the control group because of higher glucose concentration dialysis fluid use (**Table 2**).

Comparison of volume status

Hypotension was defined as SBP<90 mmHg or DBP<60 mmHg, and 30.8% of patients in the control group versus no patient in the diuretic group presented with hypotension (P<0.01). The incidences of hypokalemia and hypoproteinemia in the control group were 34.6% and 23% respectively, which was much higher than those in the diuretic group (7.7% and 3.8% respectively). At start of the observation period, the total glucose content per day in the dialysate was significantly (P<0.05) higher in the control group than it was in the diuretic group. At the end of the observation period, the blood sugar content had risen from 4.49±1.35 mmol/L to 7.72±4.05 mmol/L in the control group (P<0.05), whereas it had remained at a similar level in the diuretic group (**Table 2**).

Discussion

Fluid expansion is very common in dialysis patients, and has been correlated with the incidence of hypertension, heart failure, and high mortality rates from cardiovascular events in dialysis patients. Such status is accompanied with a gradual decline of residual renal function [22]. Hyperosmotic dialysate and diuretics are common therapies to improve the volume status in peritoneal dialysis patients. There is some evidence that both methods are effective [23]. Diuretics have no efforts in anuria dialysis patients. There are no clinical guidelines for fluid status management with diuretics and different results of the effect on residual renal function were reported in the past 20 years [18-20], so the proportion of diuretic use are 21.7% in Europe, 19.0% in Japan, and 9.9% in the US [17]. The aim of this study was to compare the influence of two different therapies on the decline of RRF in the peritoneal dialysis patients with mild or moderate fluid expand.

This study showed that high-glucose dialysis solution can dramatically improve the volume status by increasing ultrafiltration (UF). In the control group, clearance of sodium through dialysis solution was higher and the removal of fluid was more rapid, which resulted in improvement of hypertension and volume status. However, because of a higher average glucose concentration of dialysate, the blood glucose increased significantly. Teitelbaum I [24] showed that excess UF can lead to hypotension, prerenal azotemia, hypercoagulative state, or AKI in dialysis patients. It also increases the risk of hypopotassaemia and thrombosis. In our study, the high incidence of hypotension was found in the patients of the control group, who showed faster loss of residual renal function than another group. The higher incidence rate of hypopotassaemia was both found in this group with more dialysis ultrafiltration output than that of another group.

Diuretics can promote removal of sodium and fluid, which was also found to be helpful for hypertension control and improvement of the volume status in dialysis patients [18]. It was a new strategy for volume control in those patients a few years ago. Many longitudinal clinical studies have showed that the use of diuretic is associated with a trend toward a reduced risk of all-cause mortality [16]. However, the effect of diuretics on renal function in peritoneal dialysis patients has not been established, especially on RRF [17]. Our study showed that furosemide could improve the volume status in dialysis patients. Meanwhile, furosemide could increase the excretion of sodium and the urine volume output. But this would not be beneficial for residual renal function protection. However, our study also showed that furosemide could delay the decline of GFR when compared with a treatment by high glucose dialysate, which was less discussed in former studies. According to the high incidence of hypotension in the control group, it is suggested that excess dialysis ultrafiltration occurs in individual cases, which would result in temporary drop of renal perfusion. In addition, the short observation duration maybe account for the difference between our study and other clinical trials.

In addition, the incidence of adverse reaction such as hypokalemia and hypoproteinemia, which may have resulted from huge loss of potassium and protein from dialysis fluid flow, was higher in the control group than it was in the diuretic group. Our data also show that excess ultrafiltration in control may result in hypotension. The blood glucose concentration was raised in the control group, as the result of a large amount of sugar absorption from high glucose dialysate.

One limitation of this study is that this was not a prospective randomized study. The study duration was only 6 months, which might not have been enough to observe a final difference in RRF between the two groups.

From this study, we can conclude that diuretics have equally effective in alleviating edema, but with slower decline of residual renal function, less adverse incidence than hyperosmotic dialysate, which perhaps is a better choice in peritoneal dialysis patients with mild and moderate edema.

Disclosure of conflict of interest

None.

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