The Extracellular Water Corrected for Height Predicts Technique Survival in Peritoneal Dialysis Patient

Boya Göre Düzeltilen Ekstrasellüler Su Oranı Periton Diyaliz Hastalarında Teknik Sağkalımı Öngörmektedir

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ABSTRACT

OBJECTIVE: Most patients on peritoneal dialysis (PD) consume a normal Western diet that contains a large amount of salt. This causes increase in extracellular volume ("fluid overload") that has to be removed mostly with the dialysis fluid, as residual renal function (if present) cannot cope with it. In the present study, we prospectively investigated whether an increased extracellular volume (corrected for height) predicted technique survival in PD patients.

MATERIAL and METHODS: Ninety-five prevalent PD patients from one center (mean age 50±13 years, 10 of them diabetic) were studied. Extracellular water (ECW), total body water (TBW), and intracellular water (ICW) were measured by multi-frequency bioimpedance analysis (m-BIA). Echocardiography was performed in all patients. Volume status was also evaluated by measuring left atrium diameter (LAD) and left ventricular end-diastolic diameter (LVEDD). Demographical, biochemical analyses, peritoneal equilibration test, weekly total Kt/V urea and weekly total creatinine clearance (CCr) results were obtained from patient chart. We identified a cut-off value for ECW/height by drawing ROC curves that differentiate patients with FO and those without, using LAD and LVEDD measured by echocardiography as confirmatory parameters. Technique survival (TS) was defined as the time on PD treatment until transfer to hemodialysis. Technique survival (TS) was assessed at the end of the follow-up and significant predictors of technique survival were investigated.

RESULTS: During the follow-up, 62 patients dropped out. Thirty-six patients were switched to hemodialysis (severe peritonitis in twelve, hernia in one, peritoneal leaks in five, inadequate dialysis in seventeen and unwillingness in one patient), twelve patients received transplants, five patients were transferred to other center and nine patients died (4 patients from infection, 4 patients from cardiovascular disease and 1 patient from malignancy). Patients switched to hemodialysis were older and had higher duration of PD treatment, body mass index, ECW/height and LAD than patients that stayed on PD. Patients that switched to HD also had significantly lower weekly total KT/V_{urea}, weekly total CCr and daily total urine volume than patients that stayed on PD.

On ROC analysis, we found a cut-off value for ECW/height of 10.5 liters/m with specificity of 78 % and sensitivity of 75% for the diagnosis of FO. Patients with the ratio of ECW/height values above the cut-off values had significantly worse technique survival than those with ECW/height below 10.5 L/m (mean survival, 28.7±2.6 vs. 35.1± 1.9 months; p=0.016). On multivariate analysis, weekly total CCr, serum CRP level and ECW/height above 10.5 L/m were independent predictors of technique failure.

CONCLUSION: An increased extracellular volume corrected for height as a fluid overload marker is associated with decreased technique survival in PD patients.

KEY WORDS: Bioimpedance analysis, Fluid overload, Technique survival, Peritoneal dialysis

ÖZ

AMAÇ: Biz prospektif olarak, periton diyalizi(PD) hastalarında artmış ekstrasellüler suyun (boya göre düzeltilmiş) teknik sağkalımı öngörüp öngöremeyeceğini araştırdık.

GEREÇ ve YÖNTEMLER: Çalışmaya halen PD'ine devam etmekte olan doksan beş hasta alındı. Ekstrasellüler su (ESS) miktarı çok frekanslı biyoimpedans cihazı ile ölçüldü.Volüm durumu ekokardiyografi ile ölçülen sol atriyum (SA) ve sol ventrikül endiyastolik (SVED) çap ölçümü ile

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değerlendirildi. Demografik ve biyokimyasal analiz sonuçları hasta dosyalarından elde edildi. Sıvı yükü olan ve olmayan hastaları ESS/boy oranına göre ayırt etmek için ROC analizinde ekokardiyografi ile ölçülen SA ve SVED çapları doğrulayıcı parametre olarak kullanılarak ESS/boy için en iyi eşik değer saptandı. İzlem sonu teknik sağkalım değerlendirildi.

BULGULAR: İzlemde 62 hasta PD'inden çıktı. Bunlardan 36 tanesi hemodiyalize geçti, 12 hasta böbrek nakli, 5 hasta başka merkeze gitti ve 9 hasta öldü. ROC analizinde sıvı yüklenmesi için ESS/boy eşik değerini 10.5 lt/m olarak bulduk. Eşik değerin üstünde ESS/boy oranına sahip olan hastaların teknik sağkalımı eşik değerin altında olan hastalara göre daha kötüydü (p=0.016). Çok değişkenli analizde, haftalık total kreatinin klirensi, serum CRP düzeyi ve eşik değerin üstündeki ESS/boy oranı teknik sağkalımın bağımsız öngörücüleri olarak bulundu.

SONUÇ: Sıvı yüklenmesinin göstergesi olarak artmış ESS/boy oranı, PD hastalarında azalmış teknik sağkalım ile ilişkilidir.

ANAHTAR SÖZCÜKLER: Biyoimpedans analizi, Sıvı yüklenmesi, Teknik sağkalım, Periton diyalizi

INTRODUCTION

Chronic fluid overload (FO) is frequently present in peritoneal dialysis (PD) patients and often together with technique failure. Technique failure was defined as transfer to hemodialysis therapy because of peritonitis, ultrafiltration failure, inadequate dialysis, exit-site and/or tunnel infection, and mechanical problems.

Volume expansion is associated with a loss of residual renal function (RRF) and leads to hypertension and left ventricular hypertrophy accompanied with increased cardiovascular morbidity and mortality in PD patients (1). When RRF is lost, removal of sodium by the peritoneal ultrafiltration is the only regulator for ingested sodium. There are many strategies useful to manage hypertension in case of RRF loss, such as dietary salt restriction, increasing the use of hypertonic glucose solutions, and addition to the use of daytime exchange in automated PD patients. Many studies have shown that ultrafiltration (UF) failure was a leading cause of PD dropout (2-4). The impaired UF capacity aggravates the volume expansion and consequent poor survival rate despite having good urea and creatinine clearance.

Subclinical volume expansion is frequent in patients on PD and assessment of hydration is not easy particularly if blood pressure is within normal limits and clinical signs of hypervolemia are not apparent. There is obviously a need for a practical method for routine clinical assessment of FO. The multi-frequency bioimpedance analysis (m-BIA) technique offers an easily repeatable, economical and non-invasive method of body composition analysis (5). The indices obtained from m-BIA are useful for evaluation of both the hydration status and nutritional status. We recently showed that the indices obtained from m-BIA, especially extracellular water (ECW) corrected for height, seem to be useful in the management of PD patients (6). In the present study, we investigated whether an increased ECW (corrected for height) predicted technique survival in PD patients.

PATIENTS and METHODS

Ninety-five PD patients treated at the Ege University Dialysis Center were enrolled in the study between November 2006 and December 2008. Inclusion criteria were patients above 18 years and dialysis vintage more than 6 months. Exclusion criteria were contraindication to magnetic resonance imaging (including presence of a pacemaker, defibrillator, ferromagnetic cerebral aneurysm clips, cochlear implants or eye prosthesis, neurostimulators, shrapnel in vital locations), previous amputation, life or technique expectancy < 1 year, pregnancy, and peritonitis in the previous 3 months. Of these patients 72 received continuous ambulatory peritoneal dialysis (CAPD) and 23 automated peritoneal dialysis. The demographic and clinical data were collected from the medical records. Anuria was defined as diuresis less than 100 ml/day. The blood samples for biochemical analysis were obtained at the time of PET (Peritoneal Equilibration Test) and the multi-frequency bioimpedance analysis (m-BIA) measurements.

In this study, we investigated the effect of ECW/height on treatment outcome at 3 years from the time of bioelectric impedance measurement. Patients were classified as continuing PD, transferred to hemodialysis (HD), died, or transplanted. Transplanted patients were censored at the date of transplant. The outcomes examined were patient death and death-censored technique failure. Technique failure was defined as transfer to HD. If a patient died within 60 days after transfer to hemodialysis, the death was attributed to PD.

Bioimpedance analysis

All patients underwent m-BIA (Bodystat Quadscan 4000, Isle of Man, British Isles) with an empty peritoneal cavity to evaluate body composition. To allow for equilibration of body fluids, patients were positioned supine for at least 15 minutes before the start of measurements with m-BIA. The following parameters were measured: ECW, total body water (TBW) and phase angle (PA) at 50 kHz. ECW values were adjusted for height. Measurements were made by the same observer, and intra-observer variability was below 2%.

Echocardiography

Echocardiography was performed in all patients. All echocardiographic measurements were performed according to American Society of Echocardiography recommendations (7-8).

The following measurements were taken: left atrium diameter (LAD), left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters, right ventricular end-diastolic diameter, thickness of the posterior wall and interventricular septum. Left ventricular mass (LVM) was calculated using the equation described by Devereux (9). Left ventricular mass index (LVMI) was calculated by dividing LVM by body surface area. LAD was adjusted for height. All measurements were made by the same operator.

Statistical Analysis

Data are presented as mean±standard deviation (SD). Proportions were compared by Chi-square analysis. Student t-test, analysis of variance and Mann-Whitney tests were used for group comparison. Correlations were sought by Pearson's test.

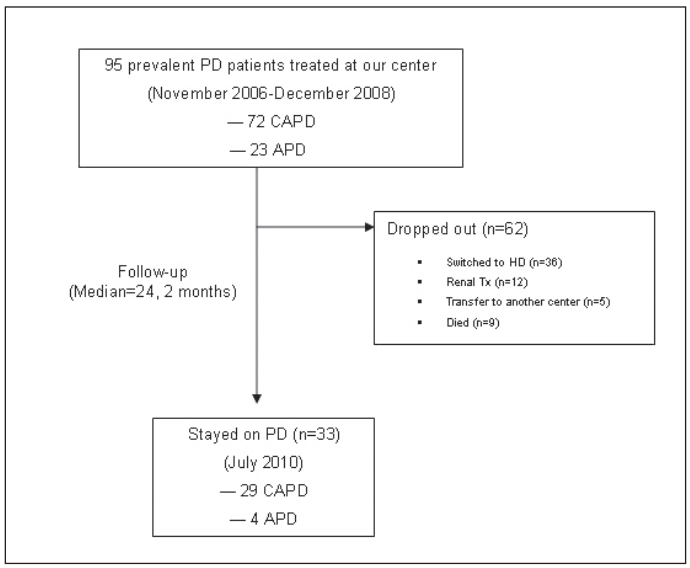

Figure 1: *Flow chart of the study patients.*

We sought the best cut-off threshold value for ECW/height by drawing ROC curves to discriminate patients with FO and those without, using LAD (>40 mm) or LVEDD (>55 mm) measured by echocardiography as confirmatory parameters. Patient groups were defined according to values above and below the cut-off value for the parameter of ECW/height. For each parameter, Kaplan–Meier survival with log rank analysis of significance was used to analyze technique survival (TS) between groups. Each parameter was also tested as a continuous variable in univariate Cox regression analysis for association with technique survival. Parameters associated with technique survival as either categorical (i.e., above vs below cut-off) or as continuous variables were entered into a multivariate Cox regression analysis. Median follow-up was 24.2 months.

RESULTS

Ninety-five patients were enrolled, with a median follow-up of 25±13 months. Mean age was 50±13 years, duration of PD 38±31 months, percentage of males 44%, and prevalence of diabetes 10.5%. Thirty-eight percent of the patients were anuric and 22 patients were on APD therapy.

During the median 24.2 months follow-up, 62 patients dropped out. Thirty-six patients were switched to hemodialysis (HD) due to severe peritonitis in 12, hernia in 1, peritoneal leaks in 5, inadequate dialysis in 17 and unwillingness in 1 patient. Twelve patients received transplants, 5 patients were transferred to another center and 9 patients died (4 from infection, 4 from cardiovascular disease and 1 from malignancy) (Figure 1). Demographic and clinical characteristics of all patients, the patients remaining on peritoneal dialysis, and patients transferring to HD are shown in Table I. When we compared these two groups, patients switched to HD were older and had higher duration of PD treatment, body mass index (BMI), ECW/height and LAD than patients that stayed on PD. Patients

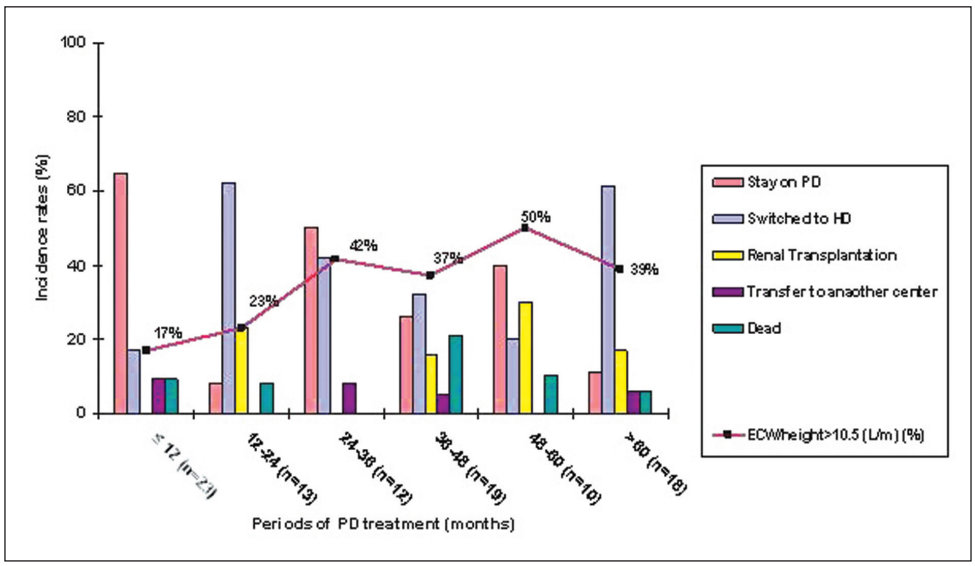

Figure 2: *Incidence rates for dropout from peritoneal dialysis and fluid overload during six periods of follow-up.*

Table I: Baseline characteristics.

	All (n=95)	Stayed on PD (n=33)	Switched to HD (n=36)	p
Age	50±13	47±14	55±11	0.007
Gender (male, %)	44	33	47	0.241
Duration of PD (months)	38±31	25±21	47±38	0.006
Body mass index (kg/m^2)	26±3	25±3	27±4	0.031
Diabetes mellitus (n)	10	3	6	0.351
anuri (%)	37.9	27.3	47.2	0.088
APD (%)	24.2	12.1	36.1	0.021
Mean SBP (mmHg)	118±22	118±22	124±25	0.297
Mean DBP (mmHg)	76±12	77±13	76±11	0.747
Weekly total Kt/V$_{urea}$	2.40±0.63	2.78±0.82	2.19±0.37	0.000
Weekly total CCr (L/1.73m^2)	75±37	94±50	64±18	0.003
Peritoneal ultrafiltration (mL/d)	1154±641	1252±631	1154±651	0.530
Residual urine volume (mL/d)	600±792	900±987	440±596	0.022
Total sodium removal (mEq/d)	171±105	204±110	154±87	0.050
Albumin (g/dL)	3.91±0.47	3.92±0.52	3.86±0.41	0.579
CRP (mg/dL)	0.96±1.97	0.57±0.96	1.41±2.92	0.109
Total cholesterol (mg/dL)	213±43	225±45	206±42	0.076
Triglyceride (mg/dL)	195±116	208±149	192±93	0.590
PA (°)	5.83±1.21	6.09±1.22	5.52±1.25	0.065
ECW (L)	16.0±2.1	15.4±2.0	16.5±2.0	0.025
ECW/height (L/m)	10.01±1.04	9.7±0.9	10.2±1.0	0.017
LAD (mm)	34±6	32±5	36±6	0.003
LAD/height (mm/m)	0.21±0.04	0.20±0.03	0.22±0.03	0.011
LVMI (g/m^2)	108±36	101±36	112±38	0.294

APD: automated peritoneal dialysis, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure, **CCr:** Creatinine Clearence, **CRP:** C-Reactive Protein, **PA:** phase angle at 50 kHz, **ECW:** Extracellular water, **LAD:** left atrium diameter, **LVMI:** left ventricular mass index

switched to HD also had significantly lower weekly total KT/V$_{urea}$, weekly total creatinine clearance (CCr) and daily total urine volume than patients stayed on PD.

Our previous study (6) identified a cut-off value for ECW/height by drawing ROC curves to discriminate patients with fluid overload and those without. This study was conducted on the patient population and we therefore used an ECW/height cut-off value of 10.5 L/m (with a specificity of 78% and sensitivity of 75%). We then evaluated the TS by dividing the patients into two groups as those with ECW/height values above (n=31) and below (n=64) 10.5 L/m. We also divided the study population into six periods according to the duration of PD treatment and calculated the percentage of drop-outs in more detail together with the percentage of patients with ECW/height values above 10.5 L/m in each period (Figure 2). These results showed that fluid overload increases after two years of PD treatment and is accompanied by decreasing daily urine output (Figure 3).

Survival Analysis

Kaplan-Meier analysis showed that patients with ECW/height above 10.5 L/m had significantly worse TS than those with ECW/height below 10.5L/m (mean survival, 28.7±2.6 vs. 35.1± 1.9 months; p=0.016) (Figure 4). Comparison of anuric patients with those with residual renal function showed that anuric patients had worse TS than those with residual renal

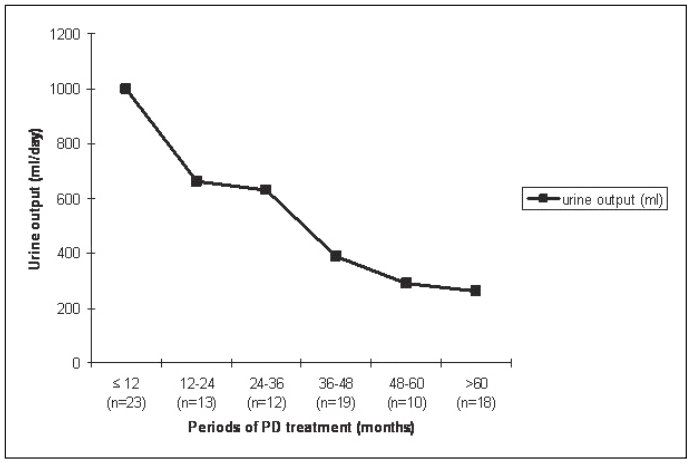

Figure 3: *Daily mean urine output during six periods of follow-up.*

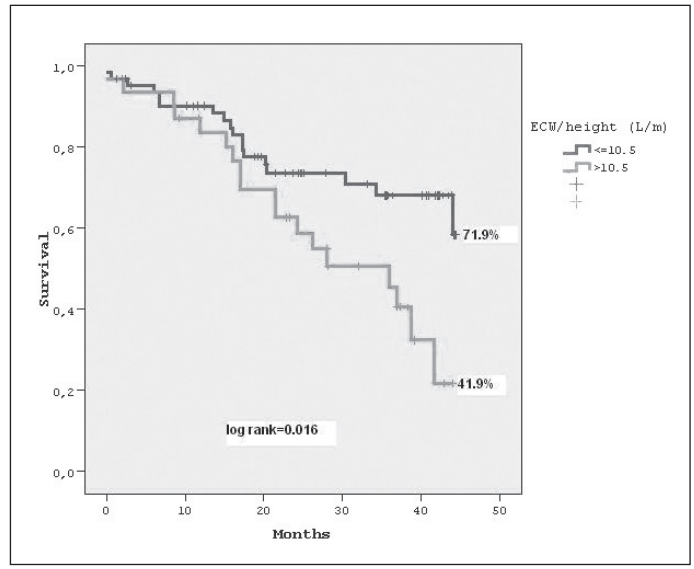

Figure 4: *Technique survival analysis performed by Kaplan-Meier method. There was significant difference in unadjusted technique survival between patients with ECW/height ≤ 10.5 L/m and patients with ECW/height>10.5 L/m, p<0.05, the log-rank test.*

Table II: RR of technique survival in univariate Cox regression for selected variables at baselin in 95 PD patients.

	RR	95% CI	P-value
Age (1 year)	1.031	1.005-1.058	0.017
Gender (female)	0.806	0.417-1.557	0.521
Previous months on PD (1 month)	1.009	1.001-1.018	0.031
Diabetic status (present)	1.975	0.819-4.759	0.129
BMI category			
18-25kg/m2	Ref	Ref	Ref
25 to 30kg/m2	1.760	0.815-3.801	0.150
>30kg/m2	2.744	1.133-6.649	0.025
PET (high vs.low)	2.128	1.073-4.218	0.031
CCr (1L/week/1.73m2)	0.981	0.966-0.997	0.019
Residual urine output (no vs yes)	0.536	0.278-1.034	0.063
Serum albumin(1g/L)	0.831	0.413-1.670	0.603
Serum CRP (1mg/dL)	1.204	1.079-1.343	0.001
UF rate (100mL/24 h)	1.00	0.999-1.000	0.804
Previous history of peritonitis (yes vs no)	0.958	0.496-1.851	0.898
ECW/height (>10.5 L/m vs. ≤ 10.5 L/m)	2.202	1.139-4.255	0.019

BMI: body mass index, **PET:** Peritoneal transport test, **CCr:** Creatinine Clearence, **CRP:** C-Reactive Protein, **UF:** ultrafiltration, **ECW:** Extracellular water

Table III: Multivariate Cox regression analysis showing independent predictors of technique survival in 95 PD patients followed up for a median 24.2 months.

	RR	95% CI	P-value
CCr (1L/week/1.73m2)	0.981	0.965-0.997	0.019
Serum CRP (1mg/dL)	1.202	1.067-1.355	0.003
ECW/height (>10.5 L/m vs. ≤ 10.5 L/m)	2.332	1.202-4.526	0.012

CCr: Creatinine Clearence, **CRP:** C-Reactive Protein, **UF:** ultrafiltration, **ECW:** Extracellular water

Table IV: The influence of fluid overload on different PD modalities survival.

ECW/height (L/m)	PD Modality	N	N of Events	Survival (%)	Log Rank
≤10.5	CAPD	51	14	72.5 %	0.811
	APD	13	4	69.2%	
	Overall	64	18	71.9%	
>10.5	CAPD	21	9	57.1%	0.004
	APD	10	9	10%	
	Overall	31	18	41.9%	
Overall	Overall	95	36	62.1%	

ECW: Extracellular water, **CAPD:** Continous ambulatory peritoneal dialysis, **APD:** Automated peritoneal dialysi

function but the difference did not reach statistical significance (mean survival, 28.3±2.9 vs. 35.6±1.7 months; p=0.058). Patient survival was not different between groups (p=0.903). The relative risks (RR) of TS were associated with age, previous months on PD, BMI, peritoneal transport status, CCr, serum C reactive protein (CRP) level and ECW/height in univariate Cox regression analysis (Table II). In multivariate analysis, CCr, serum CRP level and ECW/height above 10.5L/m were independent predictors of technique failure (Table III).

We also examined the influence of fluid overload on different PD modality technique failure and we saw that patients with fluid overload on APD treatment had significantly worse TS than patients on CAPD treatment. However, this PD modality difference effect on TS was not significant in patients without fluid overload (Table IV).

DISCUSSION

Fluid overload is common problem in PD patients and over time PD patients may progressively develop fluid retention due to loss of residual urine volume and incompliance with salt restriction. Therefore, technique failure due to inadequate fluid removal and hypervolemia is increased. As we have shown in a previous study (6), ECW/height obtained by bioimpedance analysis seems to be a useful and practical method for routine clinical assessment of fluid overload in PD patients. In this study, we found that an increased ECW/height as a fluid overload marker is associated with decreased technique survival in PD patients. In another study with a limited number of patients, it was found that increased ratio of extracellular fluid volume to total body water is associated with decreased TS in PD patients. On multivariate analysis, systolic blood pressure and extracellular fluid volume to total body water were significant predictors of TS (10). In our previous study (6), the ECW/TBW ratio was not a good index for the evaluation of fluid overload in ROC curves and it reflected inflammation rather than volume overload. We therefore did not use this index for evaluating volume status. In a recent large retrospective study, TS was significantly lower in patients with a higher incidence of peritonitis and the episodes of peritonitis were the only factor independently associated with TS (11). In our study, peritonitis was not associated with TS.

In recent years, there has been increased interest in the use of biocompatible PD solutions due to improved volume control by better preservation of residual renal function and higher degree of biocompatible and favorable metabolic effects. In one study, icodextrin use was found to be associated with lower TS and this was attributed to improved volume control but volume status was not evaluated by any method (12). In one randomized clinical study, icodextrin use increased technique survival rate in PD patients with diabetic nephropathy by increasing ultrafiltration volume (13). In another observational study, the use of biocompatible PD solutions with physiological pH was associated with improved survival compared with conventional study, but they did not find any difference in TS (14). Srivastava et al. conducted a randomized controlled study comparing the

use of biocompatible solutions and conventional solutions and showed no difference in peritonitis or TS between groups (15). In our study population, we did not evaluate the influence of the use of biocompatible PD solutions on TS because we did not have a sufficient number of patients to evaluate this effect.

The influence of fluid removal on patient and technique survival was studied in PD patients (16). In one study, patients with moderate total fluid removal both at baseline and throughout their PD treatment showed improved TS (17). Lin et al. showed that daily peritoneal ultrafiltration over 1L/day was associated with better TS compared to daily peritoneal ultrafiltration lower than 1L/day and attributed this to better fluid balance (18). Similarly, we found that patients with fluid overload had worse TS than patients without. The decreasing weekly total creatinine clearance, increasing inflammation and fluid overload were independent predictors of TS in our study population. A reduction in renal function may aggravate the inflammatory state due to decreased renal clearance of cytokines. In our study, patients with anuria had higher serum CRP levels that may be explained with this hypothesis.

Studies on the relationship between peritoneal transport status and TS in the literature report controversial results. In one meta-analysis, a higher peritoneal membrane solute transport rate was associated with higher mortality risk and a trend to higher technique failure (19). In another large study, it was found that the outcomes of CAPD and APD were similar (20). Recently, Balasubramanian et al. showed that there was no difference in TS between these modalities (21). Similarly, in one large prospective cohort study, it was reported that there was no difference in overall mortality and technique failure for APD compared with CAPD in incident dialysis patients (22). Consistent with the findings in these studies, we found that TS rates were similar in patients without fluid overload whether on CAPD or APD treatment. However, patients with fluid overload and on APD treatment had significantly worse technique survival than patients on CAPD treatment.

In PD patients, the incidence of technique failure is highest during the earliest months of PD treatment due to catheter and abdominal complications and decreases later (23). In our study, the incidence of technique failure was highest in the early period and latest period of PD treatment, due to mechanical problems and fluid overload respectively.

Loss of residual urine output in over time and fluid overload may become clinically apparent in some patients but not all. We consider that ensuring better fluid balance by ultrafiltration and restricting salt consumption are important issues in the management of PD patients especially when residual renal function is lost. In this stage, determination of fluid overload with bioimpedance analysis (especially using ECW/height) may be helpful in patient management and improving technique survival.

Conflict of Interest

EO is a member of scientific board of Fresenius Medical Care, Turkey. The other authors declare no conflict of interest.

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