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Original article

Continuous Ambulatory Peritoneal Dialysis and Clinical Outcomes in Patients With Refractory Congestive Heart Failure

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ABSTRACT

Introduction and objectives: Peritoneal dialysis has been proposed as a therapeutic alternative for patients with refractory congestive heart failure. The objective of this study was to assess its effect on long-term clinical outcomes in patients with advanced heart failure and renal dysfunction.
Methods: A total of 62 patients with advanced heart failure (class III/IV), renal dysfunction (glomerular filtration<60 mL/min/1.73 m^2), persistent fluid congestion despite loop diuretic treatment and at least 2 previous hospitalizations for heart failure were invited to participate in a continuous ambulatory peritoneal dialysis program. Of these, 34 patients were excluded and adjudicated as controls. The most important reasons for exclusion were refusal to participate, inability to perform the technique and abdominal wall defects. The primary endpoint was all-cause mortality and the composite of death/readmission for heart failure. To account for baseline imbalance, a propensity score was estimated and used as a weight in all analyses.
Results: The peritoneal dialysis (n=28) and control groups (n=34) were alike in all baseline covariates. During a median follow-up of 16 months, 39 (62.9%) died, 21 (33.9%) patients were rehospitalization for heart failure, and 42 (67.8%) experienced the composite endpoint. In the propensity score-adjusted models, peritoneal dialysis (vs control group) was associated with a substantial reduction in the risk of mortality using complete follow-up (hazard ratio=0.40; 95% confidence interval, 0.21-0.75; *P*=.005), mortality using days alive and out of hospital (hazard ratio=0.39; 95% confidence interval, 0.21-0.74; *P*=.004) and the composite endpoint (hazard ratio=0.32; 95% confidence interval, 0.17-0.61; *P*=.001).
Conclusions: In refractory congestive heart failure with concomitant renal dysfunction, peritoneal dialysis was associated with long-term improvement in clinical outcomes.

Diálisis peritoneal ambulatoria continua y evolución clínica de pacientes con insuficiencia cardiaca congestiva refractaria

Palabras clave:
Diálisis peritoneal ambulatoria continua
Insuficiencia cardiaca congestiva refractaria
Insuficiencia renal
Sobrecarga de líquidos
Mortalidad
Reingreso

RESUMEN

Introducción y objetivos: Se ha propuesto el empleo de la diálisis peritoneal como alternativa para los pacientes con insuficiencia cardiaca congestiva refractaria. El objetivo de este estudio es evaluar su efecto en la evolución clínica a largo plazo de los pacientes con insuficiencia cardiaca avanzada y disfunción renal.
Métodos: Se invitó a un total de 62 pacientes, con insuficiencia cardiaca avanzada (clase III/IV), disfunción renal (filtrado glomerular < 60 ml/min/1,73 m^2), congestión persistente por exceso de líquidos a pesar del tratamiento con diuréticos de asa y al menos dos hospitalizaciones previas por insuficiencia cardiaca, a participar en un programa de diálisis peritoneal ambulatoria continua. De ellos, se excluyó a 34 y se los asignó al grupo control. Las razones de exclusión más importantes fueron la negativa a participar, la incapacidad de aplicar la técnica y la presencia de defectos de la pared abdominal. El objetivo primario fue la mortalidad por cualquier causa y la combinación de mortalidad y reingreso por insuficiencia cardiaca. Para tener en cuenta el desequilibrio existente en la situación basal, se estimó una puntuación de propensión que se utilizó como ponderación en todos los análisis.
Resultados: Los grupos de diálisis peritoneal (n = 28) y de control (n = 34) eran similares respecto a todas las covariables basales. Durante una mediana de seguimiento de 16 meses, 39 (62,9%) fallecieron, 21 (33,9%) pacientes fueron rehospitalizados por insuficiencia cardiaca y 42 (67,8%) presentaron el

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objetivo combinado. En los modelos ajustados según la puntuación de propensión, la diálisis peritoneal, comparada con el grupo control, se asoció a una reducción sustancial del riesgo de mortalidad en el seguimiento completo (razón de riesgos = 0,40; intervalo de confianza del 95%, 0,21-0,75; p = 0,005), la mortalidad evaluada con los días de vida fuera del hospital (razón de riesgos = 0,39; intervalo de confianza del 95%, 0,21-0,74; p = 0,004) y el objetivo combinado (razón de riesgos = 0,32; intervalo de confianza del 95%, 0,17-0,61; p = 0,001).

Conclusiones: En la insuficiencia cardiaca congestiva refractaria con disfunción renal concomitante, la diálisis peritoneal se asoció a una mejoría de la evolución clínica a largo plazo.

Abbreviations

AHF: acute heart failure
CAPD: continuous ambulatory peritoneal dialysis
CHF: congestive heart failure
HF: heart failure

INTRODUCTION

Systemic congestion commonly occurs in patients with advanced heart failure (HF) and is considered a hallmark in those with acute heart failure (AHF).[1] In addition, there is strong evidence suggesting that congestion may play an important role in progression of the disease.[2–4] Indeed, recent data support the role of fluid retention in the pathogenesis of renal dysfunction (cardiorenal syndrome) and subsequent diuretic resistance,[5,6] which are associated with limited therapeutic options[7,8] and poor prognosis.[9–11] In this context, 2 related procedures have been proposed for the management of these patients: *a)* intermittent ultrafiltration, which is particularly useful during episodes of acute decompensation,[12,13] and *b)* continuous ambulatory peritoneal dialysis (CAPD), which has been considered an attractive alternative for the treatment of refractory congestive heart failure (CHF) by offering a continuous and more physiological ultrafiltration process.[14–21] Indeed, our group, as well as other groups, have described patient improvement in clinical and functional status, favorable changes in echocardiographic and hemodynamic parameters, and reduction in hospitalization rates associated with the use of CAPD with an acceptable rate of adverse effects.[14–21] Nevertheless, the effect of CAPD on long-term clinical outcomes is still unknown.

The aim of this study was to compare clinical outcomes between patients included in a CAPD program vs a similar cohort of CHF patients who were eligible for CAPD but who refused to be enrolled or were excluded from the program.

METHODS

Study Group and Protocol

We prospectively studied a cohort of 62 patients, who were followed up in the HF unit of the *Hospital Clínico Universitario de Valencia* from August 1, 2008 to June 1, 2011, and who met the following inclusion criteria: *a)* at least 2 prior admissions for AHF, with the last episode being in the past 6 months; *b)* New York Heart Association (NYHA) functional class III/IV; *c)* persistent congestion despite optimal loop-diuretic therapy, and *d)* the presence of renal dysfunction documented at least once in the last 12 months (estimated glomerular filtration rate [eGFR]<60 mL/min/1.73 m^2).

AHF was defined as a rapid onset of symptoms and signs secondary to abnormal cardiac function and the presence of objective evidence of structural or functional abnormality of the heart at rest (such as cardiomegaly, third heart sound, cardiac murmur, an abnormality demonstrated by an echocardiogram or raised natriuretic peptides).[7,8]

During their last hospitalization, patients who met the inclusion criteria (n=62) were invited to participate in the CAPD program as an alternative therapeutic option for the relief of fluid overload. Of these 62 patients, 20 refused to participate or showed inability to perform the technique at home, 7 were excluded because of the presence of abdominal wall defects, and 1 patient, who was initially selected, was subsequently withdrawn to undergo a cardiac transplantation (Fig. 1). Therefore, an abdominal catheter was surgically implanted in the remaining 34 patients, at a median of 31 days [interquartile range, 2-37] since the last hospitalization. Subsequently, 6 patients did not start dialysis for various reasons listed in Figure 1. Finally, we were able to initiate CAPD in 28 patients, at a median of 58 days [40-64] since the abdominal catheter implantation. The CAPD program consisted of 2-3 times/day exchange with dialysate solution (1.36%–2.27% of glucose), the latter titrated according to the patient's response. Our protocol followed the current international guidelines on the treatment of peritoneal dialysis-related infections,[22,23] and peritoneal access.[24]

Demographic information, medical history, vital signs, 12-lead electrocardiogram, echocardiography, laboratory data and pharmacological treatments were routinely assessed using pre-established questionnaires. Concomitant use of medications for the treatment of HF was individualized according to established guidelines,[7,8] and all patients (including controls) received a similar regimen of follow-up visits. According to the protocol, the loop-diuretic dosage was not initially modified until a clinical reduction of systemic congestion was verified. The protocol was approved by the ethical committee of our center, and was in accordance with the principles of the Declaration of Helsinki and national regulations.

Treatment Intervention

Only those patients who fulfilled the inclusion criteria and underwent the CAPD procedure constituted the active treatment group (n=28). Patients who also fulfilled the inclusion criteria but were not finally enrolled in the CADP program were assigned as controls (n=34). The control group was managed according to established treatment guidelines.[7,8]

Endpoints

The primary endpoint was all-cause mortality (using complete follow-up and days alive and out of hospital [DAOH] as follow-up time) and the composite of death/readmission for AHF.

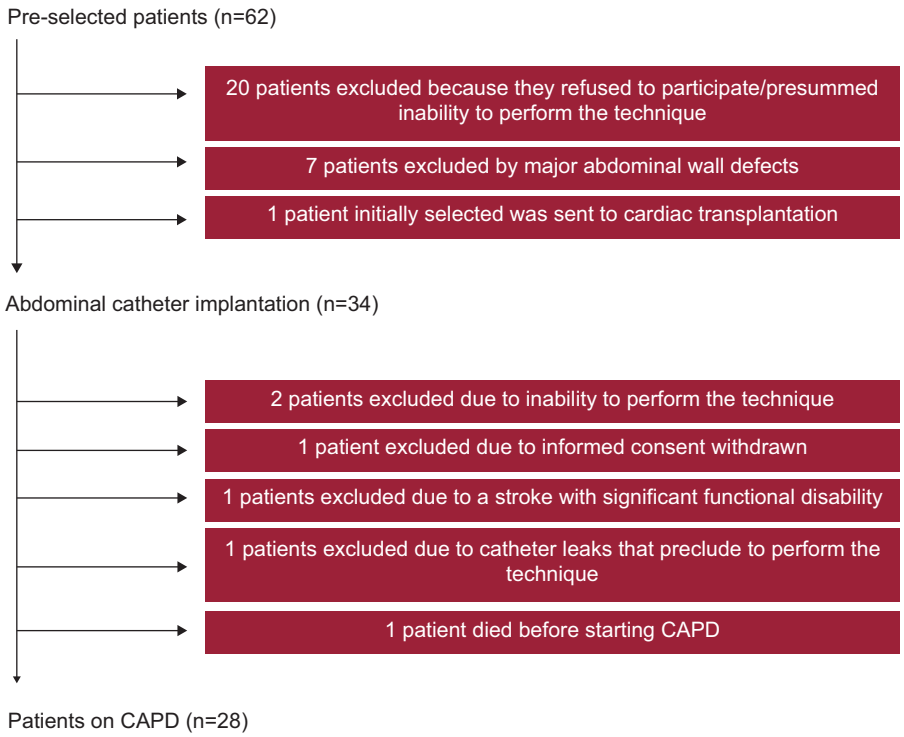

Figure 1. Flow chart. CAPD, continuous ambulatory peritoneal dialysis.

Statistical Analysis

Data analysis was performed according to the statistical analysis plan developed by Cuore International, Inc. (Scottsdale, Arizona, United States). Continuous variables were expressed as mean (1 standard deviation) or median [nterquartile range] when appropriate. Discrete variables are shown as percentages.

To estimate the causal effects of CAPD, a propensity score (PS) weighting was estimated using a boosted CART algorithm[25] implemented in R (the twangTWANG package).[26] The variables included in the PS-weighting are listed in Table 1. We used 20 000 iterations, a shrinkage parameter of 0.0005, and a stopping rule that minimizes the mean of the Kolmogorov-Smirnov test statistics. To reduce the type I error by preserving the sample size, the PS was stabilized according to: if CAPD=1, then sPS=p/PS, and if CAPD=0, then sPS=(1–p)/(1–PS), where p is the probability of treatment without considering covariates.[27] The performance of the PS was evaluated through the calculation of the standardized effect size, and by examining the spread of the PS among the treatment and comparison groups.[26] The PS was then incorporated as weights into a regression model with only the treatment as a predictor variable and no covariates. As recommended, the 95% confidence intervals (95%CIs) were estimated using "robust" standard errors (also known as the "Huber sandwich estimator").[27]

For all survival analyses, patient follow-up was censored if death or cardiac transplantation occurred during the follow-up period.

The cumulative risk for all-cause mortality (using complete follow-up and DAOH) and for the composite endpoint of mortality and AHF rehospitalization were depicted using the Kaplan-Meier method, and their differences were tested by the Cox test. The effect of the intervention was assessed by estimating a PS-weighted hazard ratio (HR) through a fitted Cox regression.

PS-weighted absolute risk differences and their reciprocal (number needed to treat) for the CAPD group were estimated from the Cox analysis, and for each clinical endpoint.[28] As recommended, these estimates were calculated at specific time points during the follow-up.[29] A 2-sided *P*-value of $<.05$ was considered to be statistically significant for all analyses. All analyses were performed using STATA 12.0 and R.

RESULTS

As part of the inclusion criteria, all patients were in NYHA class III/IV, had previous admissions for AHF and showed persistent signs and symptoms of congestion (despite treatment with loop diuretics). The mean age was 73.4 (9.2) years; 75.8% were men, and 66.1% had a prior history of ischemic heart disease. The medians for Charlson comorbidity index, eFGR, left ventricular ejection fraction, plasma N-terminal pro-brain natriuretic peptide and daily furosemide dose were 4 [3-6], 30.6 mL/min/1.73 m^2 [20-44.5], 38.5% [30%-49%], 10 703 pg/mL [5672-23 075] and 160 mg [120-160], respectively. No significant differences were observed among clinical, electrocardiographic, laboratory and medical treatment between CAPD and control patients (Table 2). The weighted comparison in baseline covariates showed an excellent balance between the 2 CAPD treatment arms (Table 1).

Clinical Outcomes Rates

Among the 62 patients initially eligible for participation in the CAPD program, there were 39 deaths (62.9%), 21 readmissions for AHF (33.9%) and 42 deaths/readmissions for AHF (67.8%) during the follow-up (at a median of 16 months [6-22]). The cause of death was identified as cardiovascular in 31 (79.5%); of these, the cause of

death was classified as death secondary to progressive HF in 18 patients.

When stratified by treatment intervention, patients who underwent CAPD showed lower rates of: *a)* death using the entire follow-up (2.81 vs 7.34 per 10 patients-year of follow-up; *P*=.004); *b)* death using DAOH (3.55 vs 9.50 per 10 patients-year of follow-up; *P*=.004); *c)* readmission for AHF (2.13 vs 5.99 per 10 patients-year of follow-up; *P*=.011), and *d)* the composite endpoint of

Table 1
Baseline Characteristics Comparison Before and After Propensity Score-weighting

	Statistics for assessing balance					
	Un-weighted			Weighted		
Variables	STD effect SZ	KS	KS *P*-value	STD effect SZ	KS	KS *P*-value
Age, years	−0.129	0.233	.260	−0.094	0.205	.405
Male	−0.034	0.015	.921	0.011	0.005	.975
Weight, kg	0.054	0.179	.578	0.026	0.175	.602
Reason for last hospitalization						
ADHF	0.139	0.057	.601	0.193	0.078	.466
Pulmonary edema	−0.268	0.099	.302	−0.348	0.128	.180
Hypertensive-related	0.284	0.036	.305	0.313	0.039	.152
Shock	0.036	0.006	.869	0.057	0.01	.717
Hypertension	0.299	0.082	.255	0.287	0.078	.283
Dyslipidemia	0.425	0.197	.103	0.347	0.161	.171
Diabetes mellitus	0.272	0.137	.291	0.184	0.093	.482
Diabetes mellitus, insulin-dependent	0.206	0.099	.419	0.111	0.053	.674
Current smoker	0.050	0.013	.889	0.028	0.007	.964
Previous smoker	−0.303	0.149	.241	−0.278	0.137	.283
Alcohol abuse	−0.106	0.023	.713	−0.113	0.025	.619
Etiology						
Ischemic heart disease	0.149	0.061	.886	0.116	0.067	.856
Valvular heart disease	0.143	0.069	.581	0.190	0.092	.461
History of MI	0.128	0.065	.610	0.057	0.029	.817
History of Stroke	−0.033	0.011	.946	−0.078	0.025	.732
History of PAD	0.262	0.116	.300	0.172	0.076	.510
History of renal failure	0.012	0.034	.844	−0.049	0.044	.741
History of COPD	0.259	0.109	.312	0.240	0.101	.354
Peripheral edema	0.195	0.069	.449	0.201	0.072	.426
Pleural effusion	0.522	0.25	.043	0.473	0.226	.071
NYHA Class III	−0.316	0.078	.244	−0.327	0.08	.251
Charlson comorbidity index	0.247	0.197	.252	0.161	0.162	.445
Heart rate, bpm	0.100	0.227	.262	0.056	0.189	.462
Systolic blood pressure, mmHg	0.050	0.174	.559	−0.006	0.15	.734
Cardiac rhythm						
Sinus rhythm	0.450	0.225	.081	0.434	0.217	.099
Atrial fibrillation	−0.263	0.126	.313	−0.222	0.106	.390
Atrial flutter	−0.108	0.023	.725	−0.137	0.029	.532
Type of BBB						
None	0.308	0.153	.231	0.208	0.103	.421
Complete LBBB	−0.457	0.221	.073	−0.410	0.198	.106
Complete RBBB	0.263	0.097	.324	0.345	0.127	.185
Pacemaker rhythm	−0.464	0.187	.074	−0.402	0.162	.119
Hemoglobin, g/dL	−0.233	0.105	.959	−0.241	0.103	.964
WBC counts, $\times 10^6$ cells/μL	0.050	0.17	.606	0.025	0.152	.744
Neutrophils, $\times 10^6$ cells/μL	−0.018	0.158	.700	−0.028	0.161	.676
Lymphocytes, $\times 10^6$ cells/μL	0.315	0.288	.101	0.226	0.233	.269
Serum creatinine, mg/dL	0.217	0.193	.465	0.143	0.171	.632
eGFR, mL/min per 1.73 m^2	0.040	0.21	.395	0.155	0.193	.502
Sodium, mEq/L	0.122	0.208	.299	0.081	0.204	.321
NT-proBNP, pg/mL	−0.217	0.181	.567	−0.205	0.184	.538
CA125, U/mL	0.024	0.214	.360	0.003	0.215	.370
LVEF, %	−0.064	0.139	.808	−0.045	0.144	.766

Table 1 *(Continued)*
Baseline Characteristics Comparison Before and After Propensity Score-weighting

	Statistics for assessing balance					
	Un-weighted			Weighted		
Variables	STD effect SZ	KS	KS *P*-value	STD effect SZ	KS	KS *P*-value
On beta-blockers	−0.164	0.082	.526	−0.144	0.072	.559
Diuretics						
On ACE inhibitor	0.070	0.036	.779	0.099	0.05	.694
On ARB	0.050	0.013	.886	0.057	0.014	.828
ICD	−0.232	0.092	.378	−0.170	0.068	.505
CRT	−0.237	0.076	.375	−0.173	0.055	.496

ACE, angiotensin converting enzyme; ADHF, acute decompensated heart failure; ARB, angiotensin II receptor blockers; BBB, bundle branch block; CA125, antigen carbohydrate 125; COPD, chronic pulmonary obstructive disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; KS, Kolmogorov-Smirnov test statistic; KS *P*-value, Kolmogorov-Smirnov associated *P*-value; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York heart association; PAD, peripheral arterial disease; RBBB, right bundle branch block; STD effect SZ, standardized effect size; WBC, white blood cell count.

Table 2
Baseline Characteristics

	Control group (n=34)	CAPD patients (n=28)	*P*
Demographic and medical history			
Age, years	77 [69-79]	75 [68-78]	.322
Male	26 (76.5)	21 (75)	1
Weight	80 [66-90]	76 [70-86]	.994
Hypertension	30 (88.2)	27 (96.4)	.366
Dyslipidemia	20 (58.8)	22 (78.6)	.112
Diabetes mellitus	10 (29.4)	11 (39.3)	.434
Current smoker	2 (5.9)	2 (7.1)	1
Previous smoker	16 (47.1)	9 (32.1)	.301
Ischemic heart disease	22 (64.7)	19 (67.9)	1
Valvular heart disease	11 (32.3)	11 (39.3)	.604
COPD	6 (17.6)	8 (28.6)	.368
Peripheral edema	28 (82.3)	25 (89.3)	.494
NYHA Class III-IV	34 (100)	28 (100)	1
Charlson comorbidity index	4 [3-6]	4.5 [4-5.5]	.334
Vital signs			
Heart rate, bpm	76 [65-90]	79 [72-100]	.419
SBP, mmHg	120 [112-140]	129 [111-150]	.656
DBP, mmHg	70 [60-80]	70 [61-80]	.814
Electrocardiography			
Atrial fibrillation	18 (52.9)	10 (35.7)	.207
QRS>120 ms	21 (61.8)	13 (46.4)	.306
LBBB	16 (47.1)	7 (25)	.113
Laboratory			
Hemoglobin, g/dL	11 [9.8-12.8]	11.1 [9.7-12.6]	.692
Serum creatinine, mg/dL	2.15 [1.42-2.78]	2.22 [1.64-3.27]	.432
Urea, mg/dL	97 [76-140]	106 [67-145]	.882
eGFR,[a] mL/min per 1.73 m^2	31 [22-49]	30 [18-39]	.404
Sodium, mEq/L	137 [135-141]	139 [136-142]	.259
NT-proBNP, pg/mL	10 703 [5672-34 837]	10 565 [5506-18 985]	.733
CA125, U/mL	60 [31-145]	86 [40-142]	.515
Echocardiography			
LVEF, %	39 [29-51]	37 [31-46]	.887
LVDD, mm	60 [53-72]	60 [50-66]	.213
PASP,[b] mmHg	47 [38-56]	52 [42-63]	.206

Table 2 *(Continued)*
Baseline Characteristics

	Control group (n=34)	CAPD patients (n=28)	*P*
Medical treatment and devices			
Beta-blockers	20 (58.8)	16 (57.1)	1
Furosemide dosage, mg	160 [120-160]	150 [120-180]	.922
Thiazide	3 (8.8)	2 (7.1)	1
Spironolactone	14 (41.2)	9 (32.1)	.599
ACEI	11 (32.3)	8 (28.6)	.788
ARB	6 (17.6)	6 (21.4)	.755
Statins	17 (50)	20 (71.4)	.120
Oral anticoagulants	15 (44.2)	14 (50)	.799
Nitrates	10 (29.4)	8 (28.6)	1
Digoxin	4 (11.8)	5 (17.9)	.719
Pacemaker	10 (29.4)	3 (10.7)	.116
ICD	8 (23.5)	4 (14.3)	.521
CRT	5 (14.7)	2 (7.14)	.442

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CA125, antigen carbohydrate 125; CAPD, chronic ambulatory peritoneal dialysis; COPD, chronic pulmonary obstructive disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; SBP, systolic blood pressure.
Data are expressed as median [interquartile range] or no. (%).
[a] Using Modification of Diet in Renal Disease formula.
[b] Data available in 51 patients.

death/readmission for AHF (3.57 vs 10.91 per 10 patients-year of follow-up; $P<.001$). Substantial differences for all-cause mortality using the entire follow-up (Fig. 2A), DAOH (Fig. 2B) and the composite of death/readmission for AHF (Fig. 2C) were observed as early as the first months, and reached their maximum around 1 year. Moreover, patients in the active treatment group showed lower rates of death from cardiovascular causes compared to controls: 8 vs. 23 patients, $P<.001$, especially ascribed to a substantial decrease in death due to HF progression (4 vs 14 patients; $P=.004$). No significant differences were observed of deaths from non-cardiovascular causes (3 vs 5 patients; $P=.493$). Among patients on CAPD, notably, only 4 deaths in the CAPD group were attributed to progressive HF while 2 of the deaths registered were due to complicated peritonitis.

Propensity Score-weighted Analyses

Table 3 shows the treatment-associated PS-weighted HR for each endpoint. Patients on CAPD displayed a significant risk reduction in all clinical endpoints as compared to the control group. The amount of risk reduction varied from 60%-70%, except for cardiovascular-related death, which showed a reduction close to 80%.

By emulating an intention-to-treat analysis, in which all patients who underwent peritoneal catheter implantation (n=34), and regardless of whether CAPD was started or not, we found that the adjusted HRs for clinical endpoints also pointed toward a prognostic benefit of CAPD. These differences were important in magnitude but did not reach statistical significance for mortality using complete follow-up (HR=0.62; 95%CI, 0.32-1.20; $P=.155$) or mortality using DAOH (HR=0.63; 95%CI, 0.32-1.22; $P=.167$) but significant for the composite of death/readmission for AHF (HR=0.52; 95%CI, 0.28-0.98; $P=.042$).

As an absolute measure of the association between CAPD and all-cause mortality, the PS-adjusted absolute risk differences and number needed to treat were estimated and depicted graphically over the follow-up time (Fig. 3). Evaluated at 1 year, we needed to treat 3-5 patients with CAPD in order to prevent 1 death or composite endpoint of death/readmission for AHF. Maximum benefits for all the outcomes were observed between the first and second year after CAPD onset.

DISCUSSION

The results of this study indicate that CAPD may play a significant role in modifying the natural history of patients with refractory CHF, in which persistent fluid overload (despite intensive diuretic therapy) and the coexistence of renal failure is also present. Indeed, the magnitude of the mortality reduction attributed to CAPD was striking in terms of relative and absolute risk reductions. A relative risk reduction of more than 50% was observed for all of the clinical endpoints, findings that were aligned with an estimated number needed to treat ranging from 3-6. Using the same cohort, our group recently showed evidence indicating that CAPD was associated with a significant and marked improvement in NYHA class, physical performance (distance walked in 6 min), quality of life (Minnesota Living With Heart Failure Questionnaire), and biochemical profile at 45 days and 180 days.[20] Notably, other groups have reported similar findings, in line with CAPD improving surrogate endpoints.[14–19] However, there are no data on the effect of CAPD on major clinical outcomes, perhaps because of the difficulty of selecting an appropriate comparison group.

To the best our knowledge, we believe this is the first study to make a formal prognostic comparison with a control group. In addition, unlike other series, our population included a non-selected population with CHF and CAPD was indicated for cardiac indications.

Ultrafiltration in Heart Failure

During the last few decades, extracorporeal ultrafiltration has been used to remove fluid from diuretic-refractory

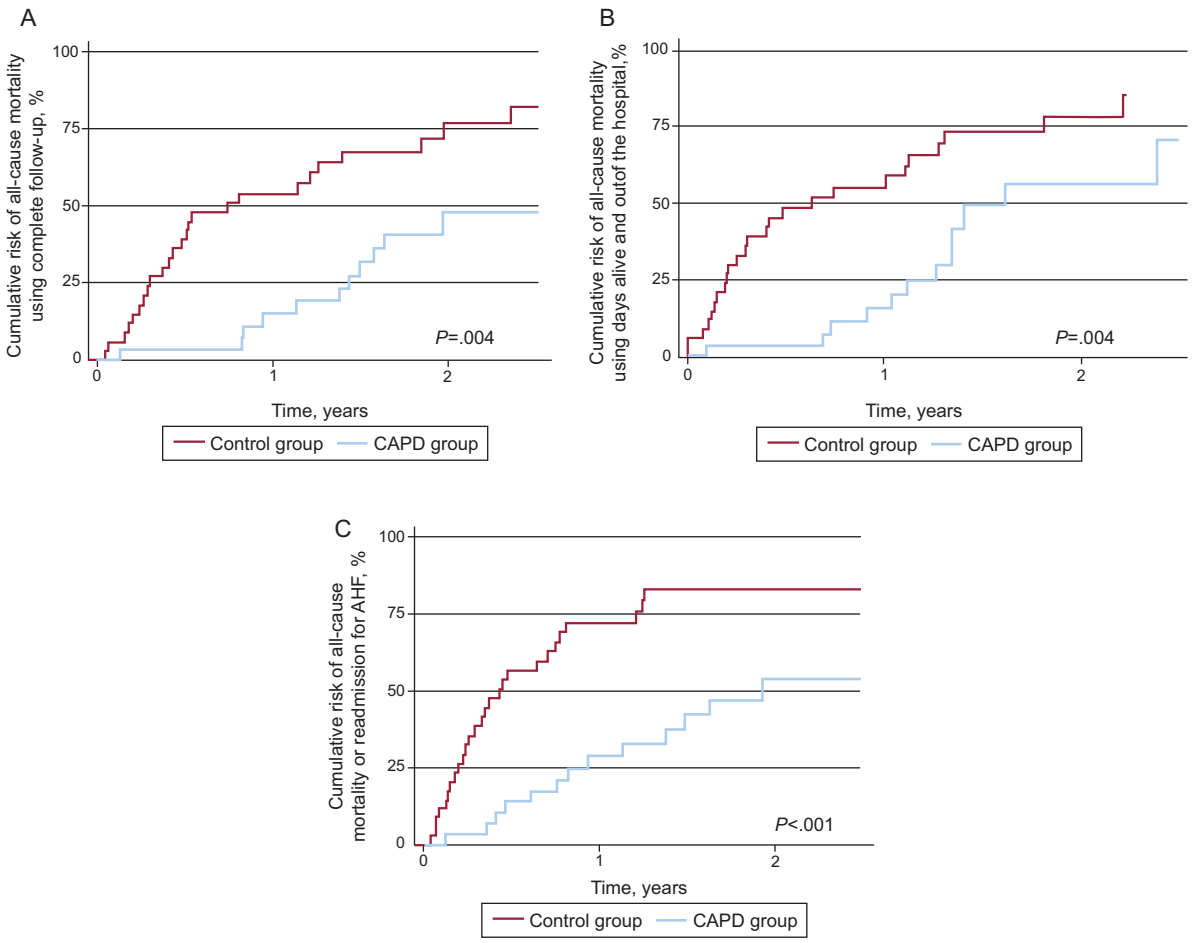

Figure 2. Cumulative incidence of all-cause mortality and the composite endpoint of all-cause mortality or readmission for acute heart failure stratified by continuous ambulatory peritoneal dialysis therapy therapy. A: All-cause mortality using complete follow-up. B: All-cause mortality using days alive and out of hospital as follow-up time. C: All-cause mortality or readmission for acute heart failure. AHF, acute heart failure; CAPD, continuous ambulatory peritoneal dialysis.

hypervolemic patients. Recent trials using user-friendly machines have been shown to be effective for decongestion of patients with fluid overload.[12,13] For instance, in patients with decompensated HF, the UNLOAD (The randomized Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated CHF) trial showed that ultrafiltration safely produces greater short-term weight and fluid loss than intravenous diuretics.[30] In addition, the group assigned to ultrafiltration showed fewer rehospitalizations at 90 days but failed to demonstrate a survival benefit.[30] In addition, the implementation of this technique requires specialized training, equipment and monitoring, limiting this approach to specific units during episodes of decompensation. Additionally, certain safety and economic issues are still a cause of concern.[12,13]

Peritoneal dialysis is a renal replacement therapy that has emerged as a therapeutic alternative for fluid overload control in patients with refractory CHF, offering a possibility of slow, daily and ambulatory ultrafiltration.

Previous Studies

Our results are consistent with various case reports and some observational studies showing the beneficial effect of CAPD on clinical, hemodynamic, biochemical and/or echocardiographic parameters.[14–19] However, most of these studies were retrospective and did not clearly define the inclusion criteria, and most of the patients included exhibited end-stage renal failure. For instance, in one of the larger studies, Gotloib et al.,[14] found a significant clinical and hemodynamic improvement 1-year after peritoneal dialysis onset in a sample of 20 patients with end-stage CHF and mean GFR=14.84 (3.8) mL/min. In contrast, patients in our cohort exhibited evidence of renal dysfunction between stages 2-4 (median eGFR=30 mL/min/1.73 m^2), at which renal replacement therapies are not currently indicated. Likewise, a recent study performed in Spain (similar to our cohort concerning GFR) reported a marked clinical (NYHA) and hemodynamic (pulmonary artery pressure) improvement associated with CAPD in 17 patients with refractory CHF.[16] In addition, these authors found similar mortality rates (life expectancy of 82% after 12 months of treatment and of 70% and 56% after 18 and 24 months, respectively) to those observed in this work (Fig. 2A). Finally, these authors reported that peritoneal dialysis was cost-effective compared with the standard treatment.[16] Recently, in 118 patients with refractory CHF included in a peritoneal dialysis program, Koch et al.[21] reported that survival rates after 3, 6, and 12 months were 77%, 71%, and 55%.

Concerning the safety of this procedure, we previously reported an elevated rate of peritonitis (1 episode every 16.18 months) as

Table 3
Continuous Ambulatory Peritoneal Dialysis and Clinical Endpoints. Adjusted Risks

	HR (95%CI)	*P*
All-cause death		
Complete follow-up	0.40 (0.21-0.75)	.005
Days alive and out of hospital	0.39 (0.21-0.74)	.004
Cardiovascular death	0.18 (0.04-0.74)	.017
Progressive heart failure death	0.29 (0.10-0.86)	.026
Combined all-cause death and rehospitalization for AHF	0.32 (0.17-0.61)	.001

95%CI, 95% confidence interval; AHF, acute heart failure; HR, hazard ratio.

compared with other contemporary large series of subjects on peritoneal dialysis[22] but similar to those observed in cardiorenal patients.[14] We believe that this finding may be attributed in part to the elevated age of our cohort, which translates into higher comorbidity scores. However, if we look at the poor prognosis in these patients (Fig. 2), the risk of peritonitis associated with the procedure seems to be acceptable, in particular when well-established therapies for these patients are absent.[7,8]

Pathophysiology

Recent evidence has highlighted the role of congestion, not only as a marker of HF severity, but also as a surrogate for complex interactions involving systemic, cardiac, renal and neurohormonal activation, processes that ultimately promote the progression of the disease.[4] For instance, the following mechanisms have been proposed as playing an important role in the pathophysiology of systemic congestion and HF progression[1–5]: *a)* neurohormonal activation (favoring sodium retention); *b)* decreased renal filtration secondary to renal venous congestion; *c)* predisposition to subendocardial cardiac ischemia; *d)* architectural ventricular modifications; *e)* endotoxin translocation, and *f)* endothelial interactions.

Along this line, we reported a substantial reduction in surrogate markers indicative of systemic and renal venous congestion in patients on CAPD.[20,31] Similarly, at 6 months after the start of CAPD, all patients in this study on CAPD, except one, tolerated furosemide reduction to 80 mg/day, following a median starting dose of 160 mg. Whether the prognostic effect attributable to CAPD in refractory CHF patients is limited to fluid overload control or there is an additional pleiotropic effect (such as clearance of inflammatory mediators) remains to be clarified.[32]

Logistic Issues

In this article we showed that CAPD may be considered a feasible alternative for the treatment of CHF patients in daily practice. Indeed, CAPD was initiated in up to 82% of patients in which an abdominal catheter was implanted. From a logistic

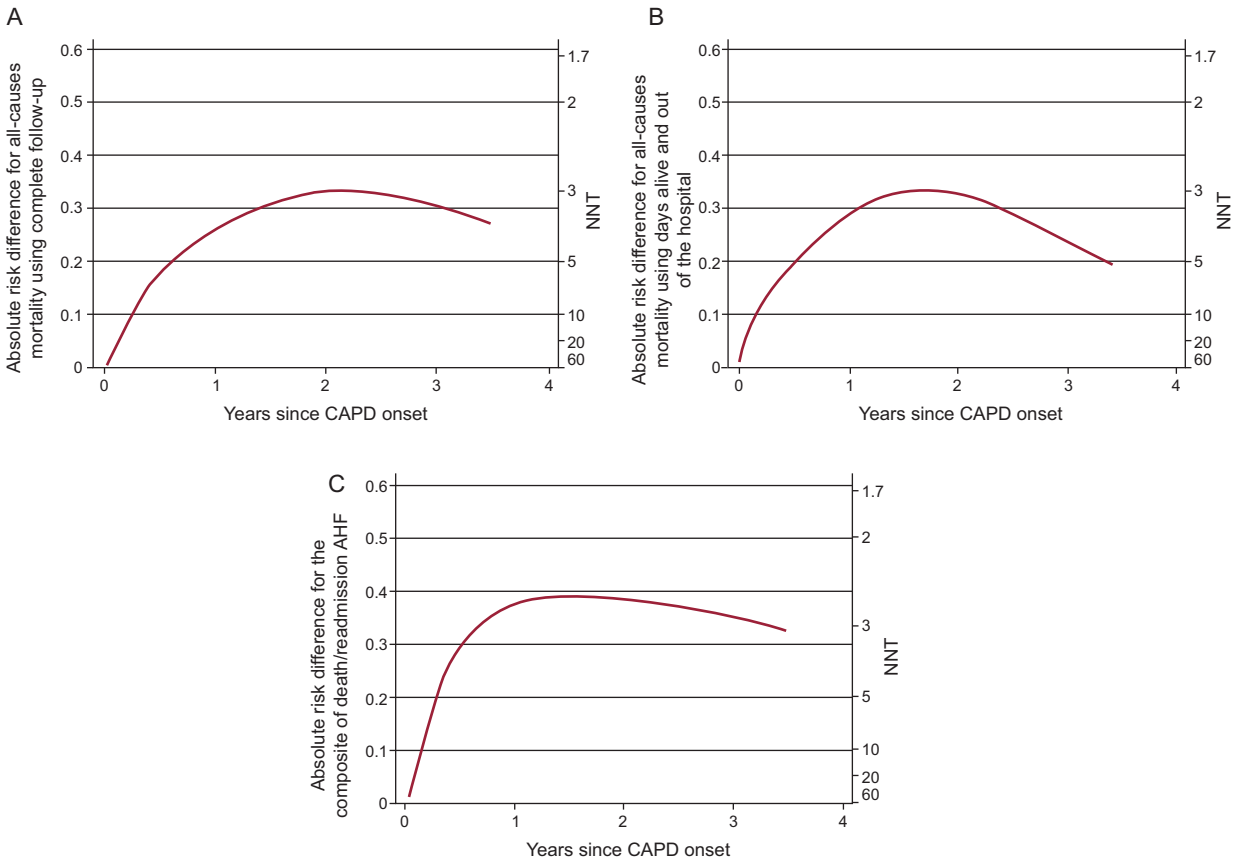

Figure 3. Absolute risk reductions and number needed to treat for time-to-event outcomes. A: All-cause mortality using complete follow-up. B: All-cause mortality using days alive and out of hospital as follow-up time. C: All-cause mortality or readmission for acute heart failure. AHF, acute heart failure; CAPD, continuous ambulatory peritoneal dialysis; NNT, number needed to treat.

perspective, CAPD offers some advantages over other ultrafiltration techniques, the most important being: slow and daily ambulatory ultrafiltration, simplicity (the procedure is easily carried out), preservation of residual renal function, and hemodynamic stability.

Limitations

The main limitation of this study stems from the fact that it is a small, single center observational study. Nevertheless, we believe that our results are sufficiently robust to have clinical significance. Even though the intervention was not randomly allocated, the control group shared similar baseline characteristics with the CAPD group, since both groups met the inclusion criteria; moreover, the use of PS-weighted regression ensured that both groups were comparable at least in all measured confounders. A randomized clinical trial in this setting would be difficult for ethical reasons, in particular owing to the difficulty of blinding the patients and the investigator to the treatment intervention.[33]

However, due to the scarce information on the efficacy, tolerability and safety of CAPD in this population of HF patients, we believe that further studies are warranted to confirm our results and to define the optimal profile of candidates for this technique and the optimal technique-logistic approach.

CONCLUSIONS

In this observational study, we found that the risk of major outcomes was significantly reduced in patients with advanced and refractory CHF and concomitant renal dysfunction who underwent CAPD. Additional studies, hopefully in more controlled scenarios, are needed to confirm these results and to define the clinical utility of this technique in this challenging subset of HF patients.

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CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail. 2010;12:423–33.
2. Colombo PC, Jorde UP. Papel activo de la congestión venosa en la fisiopatología de la insuficiencia cardiaca aguda descompensada. Rev Esp Cardiol. 2010;63:5–8.
3. Niebauer J, Volk HD, Kemp M, Dominguez M, Schumann RR, Rauchhaus M, et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet. 1999;353:1838–42.
4. Dupont M, Mullens W, Tang WH. Impact of systemic venous congestion in heart failure. Curr Heart Fail Rep. 2011;8:233–41.
5. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008;52:1527–39.
6. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol. 2009;53:589–96.
7. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al.; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29:2388–442.
8. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. Guías europeas de práctica clínica para el diagnóstico y tratamiento de la insuficiencia cardiaca aguda y crónica (2008). Version corregida 3/3/2010. Rev Esp Cardiol. 2008;61:1329.e1–70.
9. Fonarow GC, Adams Jr KF, Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA. 2005;293:572–80.
10. Giamouzis G, Kalogeropoulos AP, Georgiopoulou VV, Agha SA, Rashad MA, Laskar SR, et al. Incremental value of renal function in risk prediction with the Seattle Heart Failure Model. Am Heart J. 2009;157:299–305.
11. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol. 2006;47:1987–96.
12. Fiaccadori E, Regolisti G, Maggiore U, Parenti E, Cremaschi E, Detrenis S, et al. Ultrafiltration in heart failure. Am Heart J. 2011;161:439–49.
13. Andrade JG, Stadnick E, Virani SA. The role of peripheral ultrafiltration in the management of acute decompensated heart failure. Blood Purif. 2010;29:177–82.
14. Gotloib L, Fudin R, Yakubovich M, Vienken J. Peritoneal dialysis in refractory end-stage congestive heart failure: a challenge facing a no-win situation. Nephrol Dial Transplant. 2005;20 Suppl 7:vii32–6.
15. Cnossen TT, Kooman JP, Konings CJ, Uszko-Lencer NH, Leunissen KM, Van der Sande FM. Peritoneal dialysis in patients with primary cardiac failure complicated by renal failure. Blood Purif. 2010;30:146–52.
16. Sánchez JE, Ortega T, Rodríguez C, Díaz-Molina B, Martín M, Garcia-Cueto C, et al. Efficacy of peritoneal ultrafiltration in the treatment of refractory congestive heart failure. Nephrol Dial Transplant. 2010;25:605–10.
17. Ryckelynck JP, Lobbedez T, Valette B, Le Goff C, Mazouz O, Levaltier B, et al. Peritoneal ultrafiltration and refractory congestive heart failure. Adv Perit Dial. 1997;13:93–7.
18. Takane H, Nakamoto H, Arima H, Shoda J, Moriwaki K, Ikeda N, et al. Continuous ambulatory peritoneal dialysis is effective for patients with severe congestive heart failure. Adv Perit Dial. 2006;22:141–6.
19. Basile C, Chimienti D, Bruno A, Cocola S, Libutti P, Teutonico A, et al. Efficacy of peritoneal dialysis with icodextrin in the long-term treatment of refractory congestive heart failure. Perit Dial Int. 2009;29:116–8.
20. Núñez J, González M, Miñana G, Garcia-Ramón R, Sanchis J, Bodí V, et al. Continuous ambulatory peritoneal dialysis as a therapeutic alternative in patients with advanced congestive heart failure. Eur J Heart Fail. 2012;14:540–8.
21. Koch M, Haastert B, Kohnle M, Rump LC, Kelm M, Trapp R, et al. Peritoneal dialysis relieves clinical symptoms and is well tolerated in patients with refractory heart failure and chronic kidney disease. Eur J Heart Fail. 2012;14:530–9.
22. Piraino B, Bailie GR, Bernardini J, Boeschoten E, Gupta A, Holmes C, et al. Peritoneal dialysis-related infections recommendations: 2005 update. Perit Dial Int. 2005;25:107–31.
23. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, et al. Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int. 2010;30:393–423.
24. Figueiredo A, Goh BL, Jenkins S, Johnson DW, Mactier R, Ramalakshmi S, et al. Clinical practice guidelines for peritoneal access. Perit Dial Int. 2010;30:424–9.
25. Lee BK, Lessler J, Stuart EA. Improving propensity score weighting using machine learning. Stat Med. 2010;29:337–46.
26. Ridgeway G. Toolkit for weighting and analysis of nonequivalent groups. R package version 1.2-5. 2012. Available at: project.org/web/packages/twang/twang.pdf
27. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health. 2010;13:273–7.
28. Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. J Clin Epidemiol. 2010;63:46–55.
29. Suissa D, Brassard P, Smiechowski B, Suissa S. Number needed to treat is incorrect without proper time-related considerations. J Clin Epidemiol. 2012;65:42–6.

30. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol. 2007;49:675–83.
31. Núñez J, Miñana G, González M, Garcia-Ramón R, Sanchis J, Bodí V, et al. Antigen carbohydrate 125 in heart failure: not just a surrogate for serosal effusions? Int J Cardiol. 2011;146:473–4.
32. Zemel D, Imholz AL, De Waart DR, Dinkla C, Struijk DG, Krediet RT. Appearance of tumor necrosis factor-alpha and soluble TNF-receptors I and II in peritoneal effluent of CAPD. Kidney Int. 1994;46:1422–30.
33. Miller LE, Stewart ME. The blind leading the blind: use and misuse of blinding in randomized controlled trials. Contemp Clin Trials. 2011;32: 240–3.