Peritoneal dialysis role in heart failure treatment, experience in our center

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SUMMARY

Peritoneal dialysis is a renal replacement therapy indicated in patients with an unstable hemodynamic status. It has been used, by ultrafiltration, preferably in those patients with congestive heart failure refractory to conventional medical therapy. We present the experience of our center with five patients who were affected by severe congestive heart failure [Class IV on the New York Heart Association (NYHA) scale] and diverse stages of chronic renal failure, who received this therapy. Icodextrin has been used as an osmotic agent to induce ultrafiltration. The follow-up period ranged between 5 and 14 months (9.8 ± 3.7 months). The results that we have found are similar to those of other studies: we observed a significant improvement in quality of life and a reduction in morbidity and hospitalization rates in all our patients. But it seems to be necessary to make a prospective randomized controlled trial with more number of individuals to confirm these promising facts, to clarify the impact on the survival, and to analyze the cost-benefit for treating patients suffering from refractory, end stage congestive heart failure.

Key words: ***Peritoneal dialysis. Heart failure. Hospitalization.***

PAPEL DE LA DIÁLISIS PERITONEAL EN EL TRATMIENTO DE LA INSUFICIENCIA CARDÍACA. EXPERIENCIA EN NUESTRO CENTRO

RESUMEN

La diálisis peritoneal es una técnica sustitutiva de la función renal indicada en pacientes con inestabilidad hemodinámica. Por ello, se ha utilizado preferentemente en aquellos pacientes con insuficiencia cardíaca refractaria al tratamiento médico convencional. Presentamos la experiencia de nuestro centro con cinco pacientes que presentaban diversos grados de enfermedad renal crónica e insuficiencia cardíaca congestiva, que recibieron este tratamiento. Los resultados que hemos encontrado son superponibles a otros estudios realizados: en todos nuestros pacientes mejoró la clase funcional según la Clasificación de la New York Heart Association y disminuyeron los tiempos de hospitalización. Parece necesario realizar estudios prospectivos con mayor número de individuos para confirmar estas afirmaciones, aclarar el impacto sobre la supervivencia, y analizar el coste-beneficio.

Palabras clave: ***Diálisis peritoneal. Insuficiencia cardíaca. Hospitalización.***

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INTRODUCTION

Heart failure (HF) is an increasing cause of morbimortality and the first cause of hospital admissions in developed countries among people older than 65 years. Its prevalence doubles with each age decade and is about 10% in people older than 70 years. In Spain there are about 80,000 hospital admissions due to HF each year and it is the third death cause of cardiovascular origin, after coronary heart disease and cerebrovascular disease.[1,2]

According to American registries, more than 50% of the patients develop HF throughout the progression of their stage V Chronic Renal Disease (CRD). Eight percent of Spanish patients with CRD stages III-IV suffer from one episode of HF, functional class III-IV of the York Heart Association (NYHA) within the first follow-up year.[3]

Severe decrease of cardiac output leads to a drop in renal perfusion, decreased glomerular filtration, increased production of neuro-hornomal substances and activation of mechanisms leading to water and salt retention, which favors a state of secondary hyperaldosteronism. Thus, the kidney becomes resistant to diuretics, which makes necessary to increase their dose perpetuating renal hypoperfusion. This is a vicious circle since HF persists and CRD develops with a primary functional origin.[4-6]

There have currently been important therapeutic advances improving HF prognosis such as beta-adrenergic receptor antagonists and angiotensin converting enzyme antagonists (ACEI), as well as angiotensin receptor antagonists (ARA). The clinical management of congestive HF, focused on the excess of extracellular volume, is based upon the use of diuretics and inotropic agents. In refractory cases, ultrafiltration (UF) techniques are quite interesting.[7-9]

Continuous renal replacement therapies such as continuous veno-venous hemofiltration are generally used to manage acute volume overload situations in oliguric patients. Some groups use them as maintenance therapies even on a daily basis, although with important logistic problems, high costs, and poor results.[10]

Included among Peritoneal Dialysis (PD) indications are those patients with hemodynamic instability and significant systolic dysfunction.[11,12] There are several series in the literature, although with a small number of cases, in which it is successfully used for managing water overload that occurs in refractory HF. This indication was first described in 1949 by Schneierson.[13] Although these are short series, it seems clear that continuous ambulatory peritoneal dialysis (CAPD), such as automated peritoneal dialysis (APD), improves both the clinical state and the quality of life of these patients[14] and have successfully been used in patients with different degrees of CRD.[15] Recently, a possible mechanism of depuration of myocardium-depressing intermediate molecular weight substances, including the natriuretic atrial peptide (NAP), has been pointed out.[16]

The aim of this work is to show our center's experience about the management of patients with PD for managing refractory HF and to carry out a literature review on this topic.

MATERIAL AND METHODS

We have retrospectively studied five patients included in the PD program of the Central University Hospital of Asturias from December of 2004 to May of 2007, due to severe HF refractory to conventional therapy, functional class III-IV of the NYHA Classification, and different degrees of CRD, by calculating the estimated glomerular filtration rate (EGFR) by the MDRD-4 formula.[17]

Left ventricular (LV) systolic function, defined as the ejection fraction (EF), the size of the heart cavities, and systolic pressure of the pulmonary artery (SPPA) were determined by echocardiography. The SPPA calculation was done by measuring the velocity of the tricuspid regurgitating flow (V) and an estimate of the pressure at the right atrium (RAP), by the following formula:

$$SPPA = 4V^2 + RAP.$$

The RAP value is estimated from the distension of the inferior vena cava or the jugular pressure. The clinical progression was done according to the functional class of the NYHA classification, the heart ultrasound study, and hospitalization days. The results are expressed as mean ± SD.

RESULTS

We retrospectively present five patients, three women and two men, aged 60 ± 6.3 years (Table I). The follow-up was 13.8 ± 5.6 months. The etiology of HF varied but was always associated to pulmonary hypertension (PH), defined as SPPA > 35 mmHg while resting, or severe systolic dysfunction, defined as EF < 35 %. All had been refused for cardiac transplantation (or re-transplantation). They also had several degrees of CRD, with EGFR of 43.60 ± 27.07 mL/min/1.73 m^2. The Charlson's comorbidity index was 6 ± 1, which implies an 85% mortality rate at one year of follow-up in those individuals with and

Table I. Table summarizing our experience at the Central University Hospital of Asturias. In all patients, the hospital staying decreased and the functional level improved. Hospitalization is expressed as the number of days during the year before the start of peritoneal dialysis, and the number of days after starting on PD and thoughout the follow-up period (*Patient treated with EPO)

Gender	Female	Male	Female	Female	Male
Age	67	64	52	55	62
Etiology of HF	Rheumatic	Dilated cardiomyopathy	Reumathic. Cardiac transplant.	Ischemic cardiopathy. Diabetes.	Congenital
Renal function previous year *vs* post-PD	Cr 0.80 mg/dL; EGFR 57 mL/min/1.73 m^2 ↓ Cr 1.19 mg/dL; EGFR 24 mL/min/1.73 m^2	Cr 1.00 mg/dL; EGFR 80 mL/min/1.73 m^2 ↓ Cr 1.88 mg/dL; EGFR 28 mL/min/1.73 m^2	Cr 3.63 mg/dL; EGFR 16 mL/min/1.73 m^2 ↓ Cr 1.70 mg/dL; EGFR 33 mL/min/1.73 m^2	Cr 3.30 mg/dL; EGFR 18 mL/min/1.73 m^2 ↓ Cr 4.42 mg/dL; EGFR 11 mL/min/1.73 m^2	Cr 1.58 mg/dL; EGFR 47 mL/min/1.73 m^2 ↓ Cr 2.46 mg/dL; EGFR 28 mL/min/1.73 m^2
Level of anemia previous year *vs* post-PD	Hb 9.7 mg/dL Hb 9.3 mg/dL	Hb 8.7 mg/dL Hb 12.3 mg/dL	Hb 8.6 mg/dL Hb 12.2 mg/dL	Hb 11.2 mg/dL Hb 13.2 mg/dL*	Hb 9.1 mg/dL Hb 12.4 mg/dL
Functional class (NYHA) previous year *vs* post-PD	Improved (class IV to III)	Improved (class IV to II)	Improved (class IV to I)	Improved (class IV to I)	Improved (clase IV to II)
Echocardiogram previous year *vs* post-PD	No data	SPPA 92 to 50 mmHg	SPPA 35 to 20 mmHg	EF 35 to 45%	No change
Hospitalization (days) previous year *vs* post-PD	83 → 5	159 → 0	225 → 17	109 → 40	120 → 8
Follow-up (months)	5	15	19	18	12

Abbreviations: Cr: Creatinine; PD: Peritoneal dialysis; EF: Ejection fraction of the left ventricle; EGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; HF: Heart failure; NYHA: New York Heart Association; SPPA: Systolic pressure of the pulmonary artery.

index > .5[18] All five patients had anemia, with hemoglobin (Hb) of 9.46 ± 1.06 mg/dL, but just one patient was receiving erythropoietin (EPO) before the start of PD.

After initiating PD therapy, both the functional class and the quality of life improved, although the latter was not objectively assessed. Besides, in all of them the number of hospitalization days decreased and just one patient was admitted in one occasion due to HF. The survival is substantially higher than the expected one according to their comorbidity. Echocardiographic improvement was seen in three patients although it was not done in one patient because of early death. UF was 720 ± 216.8 mL/day. All received diuretics and EPO. Just one patient presented a peritonitis episode.

Patient 1: This is a 67 years old lady with rheumatic valvulopathy and double aortic lesion, mitral stenosis, and tricuspid stenosis, operated in 1992 with aortic valve replacement, mitral and tricuspid commissurotomies. Later on, she developed atrial fibrillation (AF) and several admissions due to HF.

The echocardiogram showed an aneurismatic right atrium, severely dilated right ventricle (ring of 67 mm), with impaired systolic function due to massive tricuspid regurgitation with lack of valves coaptation and SPPA > 40 mmHg; she also presented moderate-severe mitral regurgitation and left ventricular hypertrophy (LVH) with preserved systolic function.

She had an acceptable renal function (creatinine of 0.80 mg/dL; urea of 57 mg/dL; EGFR of 57 mL/min/1.73m^2), but anemia (Hb of 9.7 mg/dL) not receiving specific therapy. Before the presence of refractory HF class IV of the NYHA, with no other therapeutic alternative, a Tenckhoff PD catheter was placed on December of 2004, starting CAPD, with nocturnal exchange three days a week by using icodextrin solution. Furosemide and home-based oxygen therapy were kept, and EPO treatment was started. With all this, there was a clear improvement of functional capacity (class III NYHA), negative balance of 11 Kg, mean UF of 900 mL, and maintenance of residual renal function (creatinine of 1.19 mg/dL; EGFR of 24 mL/min/1.73m^2).

After five months of follow-up, she was admitted in one occasion for non-cardiac cause for two days (for

blood transfusion). During the previous year, she had been admitted to the hospital for 83 days. She suddenly died at home on May of 2005.

Patient 2: This is a 64 years old gentleman, diagnosed with dilated cardiomyopathy, AF and several admissions due to HF.

The echocardiogram showed dilated right ventricle with severe tricuspid regurgitation and PH (SPPA of 92 mmHg), with normal width of the left cavities and EF of 75%.

He was referred because of refractory HF, class IV of the NYHA, presenting normal renal function (creatinine of 1.00 mg/dL; EGFR of 80 mL/min/1.73m^2), and anemia (Hb of 8.7). He did not receive EPO therapy.

A Tenckhoff PD catheter was placed on August of 2005, starting on CAPD, at the beginning with nocturnal exchange two days a week, and progressively increasing to daily nocturnal exchange, according to the clinical situation, with icodextrin solution. Diuretics and home-based oxygen therapy were kept, maintaining an UF of 800 mL and diuresis of 1000 mL, with a clear-cut improvement of the functional class (class II of the NYHA).

The follow-up echocardiogram on June of 2006 showed moderate tricuspid regurgitation and SPPA of 50 mmHg.

The anemia was improved with EPO and residual renal function was maintained (creatinine of 1.88 mg/dL; EGFR of 28 mL/min/1.73m^2), and the patient did not need to be admitted throughout the 15 months of follow-up. During the previous year, he had been hospitalized for 159 days. He suddenly died at home on December of 2006.

Patient 3: This is a 52 years old lady with mitral rheumatic valvulopathy in 1995 and 1996, and valve replacement in 1999. Since then, she had had several admissions due to refractory HF, so that she received orthotopic cardiac transplantation on May of 2005. Before the transplant, there was a slight renal function deterioration of likely hemodynamic origin (creatinine of 1.08 mg/dL; EGFR of 57 mL/min/1.73m^2).

She had poor post-surgical course, with predominantly right HF and renal failure with an important functional component (creatinine of 3.63 mg/dL; urea of 306 mg/dL; EGFR of 16 mL/min/1.73m^2). Under a clinical situation of anasarca and oliguria, hemodialysis with UF is started on October of the same year. She had marked anemia (Hb of 8.6 mg/dL), she had received transfusions but not EPO. At that time, the echocardiogram showed LVH (14 mm), with normal EF, and severe tricuspid regurgitation with SPPA of 35 mmHg.

When the patient was stabilized, a Tenckhoff PD catheter was placed on November of 2005, starting on APD and then continuing, one month later, with CAPD with three exchanges per day, one of them with icodextrin solution, progressively decreasing the number of exchanges until October of 2006, at which time PD therapy was discontinued without functional heart deterioration and with maintained stage III CRD (creatinine of 1.7 mg/dL; EGFR of 33 mL/min/1.73m^2).

She was kept on Furosemide and EPO therapy, and we tried to control her PH with Sildenafil. [19] The UF achieved with PD was 600 mL, diuresis of 2000 mL, and clearly improved functional capacity (class I of the NYHA).

The follow-up echocardiogram done on May of 2006 showed severe tricuspid regurgitation, but decreased SPPA (20 mmHg).

She was admitted for 10 days in total throughout nineteen follow-up months, always for transplantation checkups, and on February of 2006 because of an episode of acute rejection. During the year before catheter placement, she had been admitted for 225 days in total.

She has had an episode of *Escherichia coli*-induced peritonitis on March of 2006.

Patient 4: This is a 55 years old lady, with CRD secondary to stage IV diabetic nephropathy[20] (creatinine of 3.3 mg/dL; urea of 117 mg/dL; EGFR of 18 mL/min/1.73m^2) and anemia on EPO therapy (Hb of 11.2 mg/dL). She had been diagnosed with coronary heart disease with acute myocardial infarction (AMI). In 1999, she was submitted to re-vascularization surgery and one year later to angioplasty. Cardiac catheterization performed on April of 2004 showed non-reparable three-vessel disease, with EF of 35%. The echocardiogram done on January of 2005 was reported as dilation of the left cavities and global hypokinesis.

After several admissions due to HF, Tenckhoff PD catheter was placed on December of 2005, starting on CAPD with nocturnal exchange with icodextrin, switching thereafter to a three-exchanges regimen with 2.27% dextrose, amino acids solution and icodextrin. In November of 2006 she was transferred to APD due to loss of residual renal function. Besides, she still uses Furosemide and EPO.

An UF of 400 mL and diuresis of 1800 mL were achieved with clear improvement of her functional capacity (class I of the NYHA). She still suffers from stage V CRD (creatinine of 4.42 mg/dL; creatinine clearance of 15 mL/min).

In the follow-up echocardiogram on June of 2006, the LV was still slightly enlarged, but the EF was 40%. After 18 months of follow-up, a new study showed

normal sized cavities and normal function, with an EF of 45%.

She had previously been hospitalized for 109 days, and throughout the 18 months of follow-up, this number has been reduced to 40 days. However, just an 18-days admission has been because of HF, whereas the causes for the remaining four episodes have been urine infection, chest pain, gold bladder crisis, and lower limb ulcers.

Patient 5: This is a 62 years old gentleman with tetralogy of Fallot operated at 10 and 20 years old (Blalock-Taussig and corrective surgery). He was asymptomatic for years, and he finally had several admissions due to HF and AF, at least from 1989. He was in a clinical condition of HF refractory to diuretics and inotropic drugs, with severe hypotension, and he developed moderate CRD of hemodynamic origin (creatinine of 1.58 mg/dL; urea of 95 mg/dL; EGFR of 47 mL/min/1.73m^2) and anemia (Hb 9.1 mg/dL). He did not received EPO. The echocardiogram done on May of 2006 showed severely enlarged right chambers, with severe tricuspid regurgitation due to rupture of the chordae tendineae of the anterior leaflet, with SPPA of 47 mmHg and severely impaired LV with severely impaired filling due to compression from the right ventricle. Oximetric jump was ruled out by hemodynamic study, although the patient was refused to new surgical repair due to moderate PH.

Before the inability to manage the patient, a Tenckhoff PD catheter was placed on May of 2006 and CAPD was started with nocturnal exchange with Icodextrin, and treatment with Furosemide, Sildenafil and EPO. A negative balance of more than 14 Kg was achieved, with normal blood pressure, UF of 900 mL and diuresis > 1000 mL, with clear improvement of his functional capacity. On March of 2007, we was admitted due to renal failure because of diarrhea-induced volume depletion, with partial recovery of a stable renal function (creatinine of 2.46 mg/dL; EGFR of 28 mL/min/1.73m^2).

Throughout the 12 months of follow-up, we was hospitalized for 8 days, as compared to

120 hospitalization days during the previous year. An echocardiogram done within one year of having started on PD did not show significant changes.

DISCUSSION

At least one third of the patients with HF present CRD associated to decreased cardiac output and aggressive diuretic therapy. Besides, 25% of the patients with CRD develop HF. The term «cardio-renal syndrome» is recently being applied to the presence or development of CRD in HF patients. These are usually aged patients, in which there are coexistent common pathologies such as coronary heart disease, diabetes, and arterial hypertension. All this leads to increased morbimortality and thus hospitalization.[21, 22]

The mechanism by which the patients with refractory HF improve with PD therapy is unknown. We found improvement of the echocardiographic parameters in the literature reviewed[5, 15, 23] and in three of our patients although these data should be cautiously analyzed due to inter-observer differences. It is also thought that there is higher evidence of a recovery of the response to diuretics.[24] However, there may be something else; following a prospective study on 20 patients, the larger series so far, Gotloib et al.[16] proposed a theory of peritoneal clearance of myocardium-depressing substances, with mean molecular weight between 500 and 20.000-30.000 Da, such as NAP, alpha-tumoral necrosis factor (α-TNF), myocardial depressing factor (MDF), and interleukines-1 and 6 (IL-1 and IL-6). Since NAP levels seem to be related with the mass of the LV, EF and cardiovascular mortality in dialysis patients,[25] cardiac cells apoptosis would be decreased by clearing these substances, thus improving contractility.

Another remarkable effect is the low rate of peritonitis, which can be explained by the low number of daily exchanges performed.[9, 15, 24]

In any case, besides the simplicity of the procedure, PD has unquestionable advantages as compared to other UF techniques: the drainage is continuous thus preventing hypotension that occur during intermittent UF in patients with hemodynamic instability,[12, 26, 27] and it also preserves residual renal function.[6]

About PD modality, the benefit of CAPD over APD does not seem to be clear.[28] However, it seems that nocturnal exchange with Icodextrin in patients without end-stage CRD is more physiologic, well tolerated, and may be easily done at home, which reduces both the morbidity and hospitalization, presumably improving the quality of life[6, 9] with high cost-effectiveness.[4]

Although quality of life was not assessed in a controlled way, our work is in agreement with the series revised in the literature. The decrease of the hospitalization rate and the recovery of both the functional class and the quality of life[4, 6, 15, 16, 24, 27-29] although more objective evidences of that and of the survival increase are needed. These has been observed with several degrees of CRD, even in uremic patients with stage IV CRD[20] that required full-dose PD during their clinical course and in three non-uremic patients with moderate CRD in whom the indication for PD was basically UF, with outstanding results. Anyhow, in acute situations and for

short treatments, UF with hemodialysis or continuous techniques seems preferable,[12, 24] as it happened at the beginning of our third case.

The indication for hemodialysis, hemofiltration or PD for managing water overload in HF is not, however, clearly established.[30] Currently, the debate is open and there exist a clear controversy, especially since the publication of the work by Stack et al.[31] on a sample of 134,728 patients included in the United States Data System (USRDS), and in which lower survival is observed in incident dialysis patients with coronary heart disease and HF treated with PD than those with hemodialysis, probably in relation with the body mass.

On the other hand, the anemia, caused by several factors, has a prevalence of 40%-50% in HF patients. It produces a deterioration of cardiac and renal functions, and a rapid progression to dialysis. It seems clearly evident that correcting the anemia with parenteral iron and EPO in patients with HF and CRD improves the cardiac function and the quality of life and decreases the hospitalization rate. [32] Besides, it seems that EPO protects the myocardium in ischemia-reperfusion and inhibits apoptosis in myocardiocytes, and improves the immune function in CRD.[21, 33]

Given the magnitude and severity of HF-related morbimortality at our setting, and that the studies carried out so far have a small number of patients, with heterogeneous etiologies and management, a multicenter, prospective study, applying PD to patients with refractory HF, with limited indications and in selected cases is urgently needed. The «Peritoneal Dialysis Clinical Practice Guidelines» of the Spanish Society of Nephrology state the possibility of using PD in those patients with severe systolic dysfunction (EF < 35%) and refractory HF.[34] Our proposal of possible indications to assess includes those patients with no possibility of surgical treatment and with no response to the best medical therapy available, ruling out other comorbidities that could limit the expected survival and with adequate socio-familial support. In any case, the inclusion criteria would have to be more accurately defined. The ideal candidate might be the one with minimal blood pressure and whose hemodynamic state improves with diuretics, even at the expense of developing prerenal renal failure.[23]

Besides, it seems necessary a multidisciplinary approach including the Cardiology, Internal Medicine, and Nephrology departments.[21]

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