Efficacy of peritoneal ultrafiltration in the treatment of refractory congestive heart failure

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Abstract

Background. Heart failure (HF) is a major health problem in developed countries. HF is a progressive, lethal disorder, even with adequate treatment. There exists a vicious circle in the pathophysiology of HF that perpetuates and magnifies the problem. Concomitant fluid accumulation may worsen the congestive HF, it is responsible for numerous hospitalizations and it is an important cause of mortality. In this situation, any means of fluid removal may aid in the management of these patients.

The objective of this study was to evaluate the efficacy of peritoneal dialysis (PD) in the treatment of refractory HF in terms of functional status, hospitalization and mortality. We also determined the improvement in health-related quality of life with the use of PD, and examined the economic consequences of its use.

Methods. We conducted a single centre, prospective, non-randomized study involving patients showing symptoms of congestive HF refractory to maximum tolerable drug treatment. All of them were treated with PD. We analysed physical and biochemical determinations, functional status (according to the NYHA classification) and echocardiogram parameters. Also, to determine the efficacy of the technique we compared the perceived state of health (measured by the EQ5D) to PD patients respect to those reported with conservative therapies. Finally, we carried out a cost-utility evaluation measured by the incremental cost-utility ratio between these two options.

Results. Seventeen patients (65% men, 64 ± 9 years) were included in the study, and 12 were still undergoing PD treatment at the end of the follow-up period (15 ± 9 months). All patients improved their NYHA functional status (65% two classes; the rest, one; P < 0.001), with an important improvement in their pulmonary artery systolic pressure (44 ± 12 versus 27 ± 9 mmHg; P = 0.007), but no changes in left ventricular ejection fraction. Hospitalization rates underwent a dramatic reduction (from 62 ± 16 to 11 ± 5 days/patient/year; P = 0.003) before and after PD treatment. PD treatment raised life expectancy of 82% after 12 months of treatment, and 70% and 56% after 18 and 24 months, respectively, much better outcomes than those reported about conservative therapies, which only use diverse diuretic regimens. PD was associated with a higher perception state of health than the conservative therapy (0.6727 versus 0.4305; P < 0.01). Finally, we found that PD is cost-effective compared with the conservative therapy.

Conclusions. We demonstrate that congestive HF programmes should consider offering PD in hope of seeing better functional status, reduced morbidity and mortality, better quality of life as well as reduced health care costs.

Keywords: congestive heart failure; costs; peritoneal dialysis; quality of life; ultrafiltration

Introduction

Heart failure (HF) is a major and growing health problem in developed countries. In Spain, ~1% of all people aged over 40 years have HF. Moreover, its prevalence doubles with each decade of life, being around 10% in people over 70 years old [1]. HF causes nearly 80 000 hospital admissions every year in our country; it is the most frequent cause of hospitalization among people over 65 years old, and it is responsible for 5% of all hospitalizations [2]. HF is also an important cause of mortality. In Spain, it is the third leading cause of cardiovascular mortality, just after coronary artery disease and stroke [3].

HF is a progressive, lethal disorder, even when properly treated. One of the characteristics of its pathophysiology is the existence of a vicious circle that perpetuates and magnifies the problem. As a consequence of the reduction in renal perfusion due to forward failure in patients with HF, there is an increased activation of the renin–angiotensin and sympathetic nervous systems. This leads to renal vasoconstriction and increased proximal tubular sodium and water reabsorption. Due to these phenomena, the distal sodium and water delivery is reduced, develops resistance to the effects of atrial natriuretic peptide and increases the...
sensitivity of the distal nephron to the actions of aldosterone [4]. These mechanisms explain the occurrence of diuretic resistance. The concomitant fluid accumulation may worsen the congestive HF and reduce cardiac output or the left ventricular inflow due to an increase in right ventricular diastolic volume. In addition, renal function is compromised as a result of decreased perfusion [5], and also because of the damage caused by the activation of neurohormonal systems (glomerulosclerosis and tubulointerstitial fibrosis) [6]. Some authors [7] describe the existence of the cardio-renal-anaemia syndrome due to the intimate relationship between them.

In this situation, fluid removal may aid in the management of patients with refractory HF. Some of the advantages of these therapies include an improvement in cardiac output thanks to the Frank–Starling mechanism, an increased left ventricular diastolic inflow, and an improvement in lung compliance after removal of the excess fluid [8]. Extracorporeal therapies are more frequently used for the acute and short-term management of refractory congestive HF. Peritoneal dialysis (PD) has been proposed as treatment for the long-term management of treatment-resistant congestive HF and for discharged patients [9–12]. However, only a small percentage of patients with short evolution time have been published.

The aim of this study was to evaluate the efficacy of PD in the treatment of refractory HF in terms of functional status according to the New York Heart Association (NYHA) criteria, technique complications, hospitalization and mortality. We also took into account the economic consequences of its use, since there is little information regarding this aspect. Finally, we determined the differences in the perceived state of health associated with the use of PD and the cost-utility, described as cost per quality-adjusted life year (QALY) saved.

Patients and methods

From December 2004 to November 2008, we conducted a single centre, prospective, non-randomized study involving patients who showed symptoms and signs of severe cardiac failure refractory to maximum tolerable drug treatment, including dietary fluid and salt restriction, diuretics (loop diuretics sometimes associated with thiazides and spironolactone), angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blockers (ARB), beta blockers, digoxin (in the case atrial fibrillation), sildenafil (in the case of pulmonary hypertension), erythropoiesis-stimulating agents (ESA) (in the case of anaemia) and cardiac resynchronization therapy if systolic dysfunction and biventricular dyssynchrony were present. The left ventricular ejection fraction (LVEF) evaluated by echocardiography should stay under 35%.

Patients

Twenty patients were assessed for receiving peritoneal ultrafiltration. Two of them rejected the treatment although they were informed we thought this was their best treatment option. They both died due to congestive HF 3 and 5 months later. Another patient died after PD catheter placement but before beginning the technique. PD was successfully used in the remaining 17 patients, so they were finally included in the study. All patients had data of pulmonary hypertension estimated by echocardiography. Different degrees of chronic renal failure were also present; the initial glomerular filtration rate determined from a 24-h urine collection was 35 ml/min (range 15–68). Thirty-five percent of the patients were diabetics. According to currently accepted criteria, none of these patients would have been considered as a candidate for heart transplantation. The study was reviewed and approved by the Medical Ethical Committee. All enrolled patients provided written informed consent.

Therapeutic schedule

Initially, patients with congestive HF were treated by extracorporeal ultrafiltration while the Tenckhoff catheter for PD was implanted. Thirteen patients underwent only one nocturnal icodextrin exchange (2 l). Other two patients needed two exchanges (one icodextrin and one 2.27% glucose solution bag, 2 l each), and other two patients required three exchanges (2 l of icodextrin and 1.36% and 2.27% glucose solution bags) due to different degrees of renal failure after PD therapy.

Parameters studied

Anamnesis, physical examination and routine biochemical determinations were conducted before the study started and after 3, 6 and 12 months of PD treatment. In addition, an echocardiogram was performed at baseline and after 6 months. Any possible incidences and side effects related to the treatment were also collected. Those patients who did not complete the study because of death or withdrawal of the technique were excluded from the longitudinal study, but baseline results were analysed on an intention-to-treat basis.

The following parameters were monitored in the course of the study: weight, diuresis (1/24 h), daily peritoneal ultrafiltration, glomerular filtration rate, LVEF and pulmonary artery systolic pressure (PASP), haemtocrits, functional status (NYHA criteria), total days of admission and mortality.

Assessment of quality of life

We evaluated the perceived state of health at the beginning of PD and at 6 months after the initial PD. The perceived state of health instrument used was the EQ-5D [13]. Health utility was determined by time trade-off and transformed visual analogue scale methods. We compared these data with those obtained from ‘conservative therapy’, defined as the costs derived from drug therapy, resynchronization therapy (where applicable) and hospitalization and mortality rates in patients with refractory congestive HF not treated with PD.

Cost-utility analysis

The quality-adjusted life year (QALY) [14] is a measure of disease burden, including both the quality and the quantity of life lived. It is used as a means of assessing the value for money of a medical intervention. To calculate the QALY, we multiplied the change in the utility value induced by the treatment by the duration of the treatment to provide then the number of QALYs gained.

Costs were assessed in terms of year 2007 Euros from the perspective of the Hospital. All costs incurred by the PD treatment, including patient care and hospitalization costs, were included in the study. Costs were obtained from the hospital Registry data. Fully allocated costs were determined by prospectively recording resource use for all patients.

A case–control design involving only cases may be used when in a brief period of time, the disease changes and has a high risk. The design resembles a retrospective non-randomized, cross-over study but differs in having only a sample of the base population-time. Self-matching of cases eliminates the threat of control-selection bias and increases efficiency. So, we defined two periods of time, PRE (conservative therapy) and POST treatment with PD; the latter set being the only control group available to provide the investigator with a base from which results could be compared, and the effects of the test therapy deciphered. Control treatment period was the period that occurred just before (PRE) the treatment period, while the cases were the patients receiving standard treatment. Therefore, the costs of follow-up and pre-treatment would likely be included. Costs averaged were separated by periods collected (PRE and POST). The costs of the patients before the clinical study and the costs of the patients who received PD treatment were compared.

The cost-utility was estimated by the ratio of the difference in mean costs of our intervention programme compared to the conservative therapy by the difference in their mean utility score, producing an incremental cost-effectiveness ratio, which was placed in one of the quadrants of a cost-effectiveness plane [15]. The size of the ratio was also included. New therapies in the southeast quadrant are both more effective and less costly
than their alternative. They are referred to as dominant strategies and are usually accepted as superior to the alternative.

**Statistical analysis**

All data were presented as mean ± standard deviation. Differences between two groups of continuous variables were analysed using the Mann-Whitney test. An analysis of differences between proportions was performed by means of Fisher’s exact test. Finally, a general linear model was carried out to assess any repeated measurements of the same variable. A value of $P < 0.05$ was considered statistically significant.

**Results**

Seventeen patients (11 men and 6 women) were included in the study. The mean age of this population was $64 \pm 9$ years. The aetiology of the cardiopathy was ischaemic in eight cases, valvular in four, idiopathic miocardiopathy in four and one patient showed a tetralogy of Fallot. The Charlson’s comorbidity index was $6.9 \pm 1.7$ (range 4–9).

At baseline, glomerular filtration rate ranged from 21 to 62 ml/min. Decline in GFR was supposed to be related to nephrosclerosis in eight cases, reduced renal perfusion due to hypotension (urine sodium $< 5$ mEq/l) in six cases; diabetic nephropathy in two cases and calcineurin inhibitor nephrotoxicity in one patient.

Twelve patients were still undergoing PD treatment at the end of the follow-up. The total period of follow-up ranged between 6 and 35 months (mean $\pm$ SD: 15 $\pm$ 9 months).

Six of the 17 patients initially needed overload removal by extracorporeal ultrafiltration due to symptoms of dyspnoea with radiological evidence of pulmonary venous congestion and cardiomegaly, generalized oedema and recent body weight gain over 5 kg, associated with acute kidney injury. According to the RIFLE classification, four of them were considered as failure (stage 3) and the rest as injury (stage 2). Ultrafiltration treatment was performed using a haemodialysis device (Fresenius Medical Care 4008-S monitor and polysulfone dialyser; Fresenius, Bad Homburg, Germany). The four patients in stage 3 of the RIFLE classification needed haemodialysis treatment. The rest were treated with ultrafiltration alone using a haemodialysis device. The patients needed a mean of 8 $\pm$ 5 sessions (range 5–12) to improve their symptoms, and their weight was reduced $14.3 \pm 3.4$ kg. The mean time duration was $172 \pm 22$ min/session.

The mean daily peritoneal ultrafiltration achieved with the technique was $670 \pm 225$ ml, maintaining a diuresis of $1410 \pm 475$ ml/day. There were no further changes in weight during the follow-up ($69$ kg at baseline and 71, 71 and 72 kg after 3, 6 and 12 months, respectively; $P = 0.325$). Glomerular filtration rate (GFR) did not change throughout the study (35 ml/min at baseline and 40, 35 and 27 ml/min after 3, 6 and 12 months, respectively; $P = 0.379$). Something similar occurred with the haematocrit level, dose of ESA or serum albumin (Table 1). There were no changes in diuretic usage before and after PD treatment. At the beginning, 16 patients were receiving furosemide (mean dose $104 \pm 60$ mg/day), 8 received spironolactone ($34 \pm 36$ mg/day) and only 1 torasemide ($5$ mg/day). At the end of the follow-up, 11 patients received furosemide ($100 \pm 49$ mg/day), 6 spironolactone ($31 \pm 30$ mg/day) and again, only 1 torasemide ($5$ mg/day).

According to the NYHA classification, 10 patients were in class IV and 7 in class III. All patients improved their NYHA functional status; thus, 11 patients improved two classes and the rest one in the NYHA scale ($P < 0.001$) within the first 3 months of treatment (Figure 1). Fourteen patients were stabilized in a satisfactory status, and only three patients’ functional status deteriorated after a mean time of 11 $\pm$ 4 months. The patients underwent an increment in their LVEF of around 10%, although it did not achieve significant difference; however, an important improvement in their PASP ($44 \pm 12$ versus $27 \pm 9$ mmHg; $P = 0.007$) estimated by echocardiography was found after 6 months.

Peritonitis was the only complication associated with the technique, and it was unusual in any case. There were only 0.02 episodes per patient and year at risk, less than the 0.56 episodes per patient and year at risk registered in our PD Unit Registry in 2007 ($P = 0.008$).

Morbidity, expressed as the number of hospitalization days/patient/year was compared between two periods: 12 months before the beginning of peritoneal ultrafiltration and throughout follow-up. It decreased from $62 \pm 16$ to $11 \pm 5$ days/patient/year ($P = 0.003$).

Five patients dropped out before the end of the study. One patient improved her functional status up to class I of the NYHA scale associated with a recovery of her LVEF, which allowed her to abandon the treatment. Three patients died from HF after 5, 12 and 16 months, respectively. One patient died after 22 months due to an oropharynx cancer.

The use of ultrafiltration in the PD technique revealed a life expectancy of 82% after 12 months of treatment and 70% and 56% after 18 and 24 months, respectively (Figure 2).

![Fig. 1. Evolution of NYHA functional class: in the first line are reported the NYHA functional status of the patients before PD treatment; in the second one, the NYHA functional status of the patients after PD treatment.](https://academic.oup.com/ndt/article-abstract/25/2/605/1816785)
Quality of life
Every patient completed the EQ5D questionnaire. PD was associated with a higher perceived state of health than the conservative therapy (0.6727 versus 0.4305; \( P < 0.01 \)). The baseline variables significantly correlated with lower utility scores, lower functional status, morbidity (as the number of hospitalization days) and survival.

Costing study results
Total health care costs for the PD group compared to the conservative therapy group were lower (16 440 € versus 27 551 €; \( P = 0.095 \)). Specifically, staffing and hospitalizations were significantly less costly for PD. In contrast, direct PD materials, depreciation, laboratory tests and imaging were all significantly more expensive for PD.

Cost-utility analysis
PD was associated with a higher utility than the conservative therapy (0.6727 versus 0.4305, \( P < 0.01 \)). Coupled with the lower costs of PD, the cost-utility for PD was 23 305 €/QALY, while for conservative treatment was 81 053 €/QALY (Figure 3). PD was the dominant strategy, with a difference of 46 237 € per QALY (Table 2). Figure 3 plots this result.

Discussion
In the present study, the satisfactory results obtained with peritoneal ultrafiltration demonstrate that this technique is a good management option for patients with refractory HF who develop severe oedema, need frequent admissions to hospital and have a poor prognosis.

Ultrafiltration has a fundamental place in the treatment of refractory HF. Extracorporeal modalities require an adequate infrastructure or complex devices for haemofiltration, which make it incompatible with discharged patients. PD technique is a simple choice for daily ultrafiltration. It is associated with preservation of the renal function, hemodynamic stability, sodium sieving with maintenance of normonatraemia and middle-molecule clearance. It is important that cytokines and humoral factors have been involved in the development and progression of HF, some of them with demonstrated myocardial depressant activity as atrial and brain natriuretic peptide, tumour necrosis factor-\( \alpha \) or interleukin 1 or 6 [16]. Moreover, circulating levels of atrial natriuretic peptide have been related to left ventricular mass and function, and predict overall and cardiovascular mortality [17]. All of them are middle molecular weight solutes, and the peritoneum is permeable to them. Perhaps, the removal of these depressant molecules has a positive impact on the contractile capacity of the myocardium and then, in the evolution of the patient.

Our patients got modest peritoneal ultrafiltration with the technique but possibly enough when added to urine output. Peritoneal ultrafiltration was associated with a significant improvement in functional status. After only 3 months of evolution, every patient improved his or her functional status in at least one class. Although there was an increase of 10% in LVEF, this change did not achieve significant difference. Takane [9] described a significant increase of

Table 2. Cost-utility results

<table>
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<tr>
<td>Cost</td>
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<td>Conservative treatment</td>
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Fig. 2. Kaplan–Meyer survival curve for overall mortality.

Fig. 3. Cost-utility of peritoneal dialysis: this bubble chart is plotted as follows: the difference in mean utility scores is displayed along the horizontal (x) axis, the difference in mean costs of our intervention programme compared to the conservative therapy are displayed along the vertical (y) axis. Cost-utility ratio is represented by the size of the bubbles.
40% in LVEF after 12 months of treatment with continuous ambulatory peritoneal dialysis (CAPD), in 16 patients with a treatment consisting of four daily 2 L exchanges using 1.5 or 2.5 g/dL dextrose. Hébert [10] found a 30% increase in LVEF after 7 months of treatment, also with CAPD using dextrose in 10 patients who underwent a second radionuclide ventriculogram. Our experience was developed in the ‘icodextrin era’, and only two of our patients needed CAPD. What we found was a dramatic decrease in PASP. Right ventricular dysfunction appears to be of prognostic importance only when associated with an elevated PASP; assessment of right ventricular function in patients with normal PASP does not improve risk stratification. The importance of an elevated PASP was further addressed in a prospective study of 1134 patients who underwent right heart catheterization and endomyocardial biopsy, and were followed for 4.4 years. Cappola [11] described that PASP was the most important haemodynamic predictor of death. Hence, a reduction in PASP could be associated with a better prognosis.

Like other authors, we did not find any changes in renal function or anaemia which could explain the improvement in the functional status.

This study shows that peritoneal ultrafiltration has a positive impact on the morbidity of patients with refractory HF. Both the number of admissions and the total days of admission during the treatment period are significantly lower when compared with those of the previous year. No admissions were needed due to technical problems, including peritonitis. Peritonitis rate was very low (in contrast with data published by Hébert [10]) but that probably has to do with the smaller number of peritoneal exchanges in our patients.

A worrisome circumstance is the high mortality observed in this kind of patient. It should be noted that this study has been carried out on critically ill patients. Due to severely impaired clinical situations and comorbit conditions, almost none of the patients were expected to survive more than 1 year. It has been alleged that for refractory HF patients under conservative therapies (only diuretic regimens), a 6-month mortality rate is over 50% and 1-year rate is around 74%, so palliative/hospice care and end-of-life options have been proposed [12]. With this background, any measure taken to improve that gloomy prognosis should be welcomed. The use of peritoneal ultrafiltration in our patients revealed a 12-month survival rate of 82%, and 56% after 2 years. Our data are similar to those showed by Hébert [10] and represent an important extension in survival when compared with patients under conservative therapies. Once we noticed the beneficial effect of the peritoneal ultrafiltration, we considered it unethical to maintain patients with severe symptoms of HF without this technique.

We assessed whether patients under PD therapy had a higher quality of life than similar patients receiving a conservative treatment. These results are the first utility scores from individuals intensively dialysed with peritoneal technique and support the hypothesis that PD is associated with a significantly higher quality of life. We measured utilities with the standard gamble technique, a commonly used method to measure quality of life in health economics. In contrast to instruments such as the SF-36 that measure health status, the standard gamble and other utility methods reflect an individual’s preferences for health states. Because people with similar health status may feel differently about how desirable their health condition is, utility measures tend to have greater variability than psychometric instruments, and the correlation between the two techniques has been, at best, modest. Controversy persists regarding the optimal choice of method to measure utility, as all methods are susceptible to biases. Nevertheless, the size and direction of effect in our study are of such magnitude and consistency that it is unlikely that correcting for operative biases would significantly change our results.

There were some limitations to this current survey. The sample size was small, and other centres with PD programs will need to confirm these results to ensure that this is a modality effect and not related to an unmeasured selection bias. More prospective studies of patients before and after changing modalities will also be necessary to support the conclusion that PD improves quality of life. In addition, the costs that we describe for PD are similar to those found in other Spanish studies [18].

We conclude that PD is the ‘dominant’ economy strategy (in terms of health economy) to treat patients with refractory HF, since it enhances functional status, reduces hospitalization and mortality rates, has lower costs, and improves quality of life. Congestive HF programs should consider offering PD to appropriate patients in hopes of seeing better quality of life as well as reduced health care costs.

Conflict of interest statement. None declared.

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