Prospective study on clinical effects of renal replacement therapy in treatment-resistant congestive heart failure

Trijntje T. Cnossen¹, Jeroen P. Kooman¹, Harmen P. Krepel², Constantijn J.A.M. Konings³, Nicole H.M.K. Uszko-Lencer⁴, Karel M.L. Leunissen¹ and Frank M. van der Sande¹

¹Division of Nephrology, Department of Internal Medicine, Maastricht University Medical Center +, Maastricht, The Netherlands, ²Department of Internal Medicine, Franciscus Hospital Roosendaal, Roosendaal, The Netherlands, ³Department of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands and ⁴Department of Cardiology, Maastricht University Medical Center+, Maastricht, The Netherlands

Correspondence and offprint requests to: Trijntje T. Cnossen; E-mail: ncnossen@amphia.nl

Abstract

Background/aims. Clinical outcome in cardiorenal syndrome (CRS) Type 2 and treatment with dialysis.

Methods. Prospective observational non-randomized study.

Results. Twenty-three patients were included, mean age 66 ± 21 years. Twelve (52%) patients were treated with peritoneal dialysis (PD) and 11 (48%) with intermittent haemodialysis (IHD). Median survival time after start of dialysis was 16 months. Hospitalizations for cardiovascular causes were reduced (1.4 ± 0.6 pre-dialysis versus 0.4 ± 0.6 days/patient/month post-dialysis, P = 0.000), without significant changes in hospitalization for all causes (1.8 ± 1.6 versus 2.1 ± 2.9 days/patient/month), New York Heart Association (NYHA) class (3.8 ± 0.4 at start versus 2.4 ± 0.7 after 4 months, P = 0.000, versus 2.7 ± 0.9 after 8 months, P = 0.001) and quality of life tended to improve (63 ± 21 at start, versus 41 ± 20 after 4 months, versus 51 ± 25 after 8 months; P = 0.056). Left ventricular ejection fraction did not change. The number of technical complications associated with dialysis therapy was relatively high in this population.

Conclusions. After starting dialysis for CRS, hospitalizations for cardiovascular causes were reduced, but not hospitalizations for all causes. Functional NYHA class improved and quality of life tended to improve, without evidence for a change in cardiac function. In this small study, no differences between IHD and PD were observed.

Keywords: dialysis; functional status; heart failure; hospitalization; quality of life

Introduction

The incidence of congestive heart failure (CHF) is still increasing. Continuing improvement of cardiac care has resulted in more people surviving acute cardiac diseases and consequently living longer to eventually develop heart failure. Treatment of hypervolaemic patients with CHF complicated by progressive and permanent chronic renal insufficiency, also known as the cardiorenal syndrome (CRS) Type 2, is notoriously difficult [1]. Patients may develop diuretic resistance leading to recurrent episodes of pulmonary congestion and oedema [2–4]. In patients with acute decompensated heart failure, continuous ultrafiltration resulted in a reduction in rehospitalization during a 90-day follow-up period [5]. However, this treatment modality is less suitable for chronic treatment of diuretic resistance, such as may occur during CRS Type 2.

Peritoneal dialysis (PD) has main characteristics of gradual fluid removal and extra sodium loss and offers potential advantages in patients with CRS Type 2, even when not complicated by severe renal failure [6–24]. Several small studies have shown that extracorporeal treatment may be useful in the treatment of CRS Type 2 [7–25]. In the majority of these patients, an improvement of functional status [11–22, 25] and a reduction in hospitalization were observed compared to historical data [18–25]. Recently, we performed a retrospective analysis in patients with CRS Type 2 and treated with PD [26]. Survival time after starting PD was highly variable and the
number of hospitalizations for cardiovascular causes was reduced after starting PD. Age and diabetes appeared to be significant prognostic factors, but not left ventricular ejection fraction (LVEF).

However, despite the possible advantages of PD in the treatment of diuretic-resistant CHF, in our clinics, intermittent haemodialysis (IHD) and (daily) isolated ultrafiltration are also offered, either if PD is not feasible or based on patient preference.

The aim of our study was firstly to investigate the outcome of renal replacement therapy in patients with known hypervolaemic treatment-resistant CHF complicated by renal impairment. Secondly, the effect of renal replacement therapy on hospitalization after starting dialysis was compared with the last 2 years before starting dialysis. Thirdly, functional status, echocardiographic parameters and quality of life were evaluated.

Materials and methods

In this prospective observational non-randomized study, 23 patients with CRS Type 2 were treated with PD or IHD based on clinical indication. Only patients with severe CHF accompanied by renal failure resistant to high dose intravenous diuretics were included. These were all patients in whom conservative therapy had failed to control their symptoms. Patients were included between 1 February 2008 and 1 August 2009. The end of the follow-up period was 1 April 2011.

Patient characteristics at baseline are displayed in Table 1. Mean age at the start of dialysis was 66 ± 21 years. Mean glomerular filtration rate (GFR) at baseline was 14.6 ± 12.1 mL/min (95% confidence interval 0–28.5 mL/min). Fourteen patients had chronic kidney disease (CKD) Stage V, seven patients had CKD IV and two patients had CKD III. According to clinical charts, renal failure was related to nephroangiosclerosis (n = 7), reduced renal perfusion due to hypotension (n = 14) and diabetic nephropathy (n = 2). In the absence of haematuria or significant proteinuria, kidney biopsies were in general not performed. Charlson’s comorbidity index was 4.9 ± 1.2 (range 2–7).

Fifteen patients had CHF because of ischaemic cardiomypathy, five patients had a dilated cardiomypathy, one patient had a rheumatic cardiomypathy, one patient had a restrictive cardiomypathy and one patient had a metabolic cardiomypathy due to diabetes. Most patients also had valvular disease. There were no differences between patients with different types of cardiomypathy. At the start of dialysis, all patients were receiving bumetanide (mean dose 8.1 ± 2.7 mg/day), two received spironolactone, 10 angiotensin-converting enzyme inhibitors and 15 used beta-blocking agents.

The choice for PD or haemodialysis (HD) was based on patient preference and clinical indication. However, in those patients who had to start acutely with dialysis treatment, HD was used as the starting therapy.

Generally, in our hospital, we use dialysis as a treatment option for CRS only in patients with severe renal failure and not as a routine option in patients with less advanced stages of renal failure. Eleven patients (48%) were treated with IHD and were dialysed over 4 h three times per week. Twelve patients (52%) were treated with PD. If the GFR was >10 mL/min, only icodextrin was used. In others, the combination of glucose-containing dialysis fluids and icodextrin was used. Nine patients started initially with one single night dwell of icodextrin (incremental PD) and three patients started immediately with continuous ambulatory PD. All patients used commercially available glucose- and non-glucose-containing (e.g. icodextrin) dialysis solutions (Baxter Healthcare, IRL, Dublin, Ireland).

According to the design of the study, at the start of dialysis and after 4 and 8 months, data were collected for laboratory investigations, renal function, functional status [according to the New York Heart Association (NYHA) classification] and LVEF and left ventricular end-diastolic diameter (LVEDD) by echocardiography and quality of life. Quality of life was evaluated by using the Minnesota Living with Heart Failure Questionnaire because all included patients were known to suffer from primary heart failure. Other parameters collected were comorbidity and causes of mortality. Time of dialysis, duration and causes of hospitalization and complications of dialysis were registered till the end of the follow-up period of the study.

Laboratory investigations included haemoglobin, serum albumin, plasma urea and plasma creatinine, serum C-reactive protein and NT-pro Brain Natriuretic Peptide (NT-proBNP). GFR was calculated by calculating creatinine clearance using 24-h urine collection.

The study was approved by the Ethical Committee of the Catharina Hospital Eindhoven and the other participating centres (Maastricht University Medical Center and Franciscus Hospital Roosendaal). All patients provided written informed consent.

Statistical analysis

Results are expressed as mean values and SD or median and range, where appropriate.

Survival was assessed by Kaplan–Meier survival analysis. Due to the limited number of patients, Cox regression analysis was used with only a limited number of elementary variables at baseline (age, dialysis modality, Charlson’s comorbidity index, GFR and LVEF). Parameters at baseline and after 4 and 8 months were compared using repeated measures analysis of variance (ANOVA) and, if significant, further analysed by a paired Student’s t-test. In case of data which were not normally distributed, the related-samples Friedman’s analysis was used.

![Cumulative survival](image)

**Fig. 1.** Kaplan–Meier survival curve.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the patients at baseline</th>
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<tbody>
<tr>
<td><strong>PD (%)</strong></td>
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<tr>
<td><strong>Gender (%) men</strong></td>
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<tr>
<td><strong>Age (years)</strong></td>
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<tr>
<td><strong>Diabetes (%)</strong></td>
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<td><strong>Weight (kg)</strong></td>
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<td><strong>Systolic blood pressure (mmHg)</strong></td>
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<td><strong>Diastolic blood pressure (mmHg)</strong></td>
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<td><strong>Diuresis (mL/24 h)</strong></td>
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<td><strong>GFR (mL/min)</strong></td>
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<td><strong>Haemoglobin (g/dL)</strong></td>
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<td><strong>Urea (mmol/L)</strong></td>
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<td><strong>Creatinine (μmol/L)</strong></td>
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<td><strong>Serum albumin (g/L)</strong></td>
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<td><strong>CRP (g/L)</strong></td>
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<td><strong>NT-proBNP (pmol/L)</strong></td>
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<td><strong>Charlson’s comorbidity index</strong></td>
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</table>

*Values displayed as mean ± SD. CRP, C-reactive protein.

*Haemoglobin correction factor: 0.62 g/dL = 1 mmol/L.*
A P-value of <0.05 was considered significant. All the statistical analyses were made using SPSS for Windows statistical software (release 18.0).

**Results**

Over a period of 18 months, 23 patients (6 women and 17 men) with primary treatment-resistant CHF complicated by renal impairment were included and started on dialysis. Fourteen patients (61%) started with HD in an acute setting. Some of the patients chose to remain on HD and others switched to PD. Eventually, 11 patients (48%) were treated with IHD and 12 patients (52%) with PD. The cumulative survival after starting dialysis is shown in a Kaplan–Meier survival curve (Figure 1). The median estimated survival time was 16.0 months. At the end of the follow-up period, five patients were still treated for >20 months. The cumulative survival of HD versus PD is shown in Figure 2. There were no significant differences observed between HD and PD.

Nine of the 23 patients (39%) dropped out within the follow-up period of 8 months. Seven patients (30%) died during the study period. Reasons of death were end-stage heart failure (n = 3; 13%), sudden death (n = 1; 4%), pulmonary carcinoma (n = 1; 4%), complications of diabetic foot (n = 1; 4%) and one patient developed a cardiac arrest during an IHD session (n = 1; 4%). Two patients (9%) were transferred to other dialysis centres, but duration and reasons of hospitalizations of those patients were registered throughout the total follow-up period of the study.

Hospitalization, expressed as the number of hospitalizations per patient per month, was compared between the last 2 years before starting dialysis and throughout the follow-up period (Table 2). Hospitalization time for all causes was 1.8 ± 1.6 days/patient/month before and 2.1 ± 2.9 days/patient/month after starting dialysis (P = 0.54).

Reasons for hospitalization were creation of arteriovenous fistula (AVF) (n = 4), thrombectomy of AVF, occlusion of AVF, diabetic foot followed by amputation (n = 2), hip fracture (n = 2), sigmoid carcinoma, transient ischaemic attack, necrotic peripheral vascular disease, intra-abdominal bleeding after PD catheter insertion, replacement of PD catheter (n = 3), fever of unknown origin (n = 2) and infections as primary peritonitis (n = 3), diverticulitis with secondary peritonitis, pneumonia and post-obstruction pneumonia due to pulmonary carcinoma.

Hospitalization time for cardiovascular causes declined from 1.4 ± 0.6 days/patient/month before to 0.4 ± 0.6 days/patient/month after starting dialysis (P < 0.001) (Table 2).

Complications related to PD technique were pericatheter leakage, vaginal leakage, peritonitis (n = 3), recurrent peritonitis, secondary peritonitis due to diverticulitis, abscess near insertion of catheter and migration of catheter tip (n = 3) (Table 3).

According to the NYHA classification, at baseline, 19 patients were in functional Class IV and 4 in Class III. NYHA class changed significantly during the follow-up period (P < 0.001). After 4 months, 14 (82%) of 17 patients improved in their functional status (P = 0.000), 11 (65%) patients improved two classes and the rest one class in the NYHA scale. After 8 months, there was still a significant improvement of functional status in 8 (73%) of 11 patients compared to start of dialysis (P = 0.001) (Table 4).

Quality of life was evaluated by using the Minnesota Living with Heart Failure Questionnaire where a lower score is associated with a higher quality of life. Quality of life tended to improve after starting renal replacement therapy (P = 0.056 by repeated measures ANOVA). Quality of life improved after 4 months in 12 of 16 patients. After 8 months, quality of life was still better in 7 of 11 patients than before starting dialysis (Table 4).

Echocardiography was performed in all patients before starting dialysis. Mean LVEF was 37 ± 20%. After 4 months, a second echocardiography was performed in 11 patients. The LVEF was either stable (n = 1), improved (n = 6) or aggravated (n = 4). Mean LVEF at the second echocardiography was 38 ± 20% (0.056). After 8 months, a third echocardiography was performed in six patients. Mean LVEF at the third echocardiography was 36 ± 13%.

![Fig. 2. Kaplan–Meier survival curve for PD versus HD patients.](image-url)

**Table 2.** Hospitalization during the last 2 years before dialysis and after start of dialysis

<table>
<thead>
<tr>
<th></th>
<th>Pre-dialysis</th>
<th>Post-dialysis</th>
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<tbody>
<tr>
<td>All causes (days/patient/month)</td>
<td>1.8 ± 1.6</td>
<td>2.1 ± 2.9</td>
</tr>
<tr>
<td>Cardiovascular causes (days/patient/month)*</td>
<td>1.4 ± 0.6</td>
<td>0.4 ± 0.6</td>
</tr>
<tr>
<td>All causes (number of hospitalizations)</td>
<td>0.27 ± 0.29</td>
<td>0.23 ± 0.23</td>
</tr>
<tr>
<td>Cardiovascular causes (number of hospitalizations)*</td>
<td>0.19 ± 0.25</td>
<td>0.03 ± 0.06</td>
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*Difference is significant (P < 0.001).
Discussion

The present prospective observational study has three important findings. Firstly, survival in patients with CRS Type 2 was highly variable after starting dialysis. The median survival time was 16 months, including five patients who were still undergoing dialysis for >20 months. This may be longer than expected given the fact that the mean Charlson’s comorbidity index in our population was 4.9. However, we admit that this observation is not a solid argument for a potential beneficial effect of renal replacement therapy on survival, as a randomized controlled trial with a sufficient number of patients would be needed to evaluate this aspect.

The survival in our present study (median 16 months) was comparable with the data of Elhalel-Dranitzki et al. [24], in which the mean survival was 17.3 months, including four patients who were still undergoing PD, and somewhat higher as compared to our retrospective analysis in which the median survival was 12 months [26]. In the study by Ryckelynck et al. [22], the mean survival was 12.7 months, including eight patients who were still treated with PD for >12 months. Gotloib et al. [20] treated 20 patients with CRS Type 2 with comparable mean age and GFR. Mean survival was 16 months and also longer than expected according to the mean Charlson’s comorbidity index of 7.8 at the start of dialysis. In our study, we did not observe significant differences between HD and PD due to insufficient power. However, when looking to both survival curves in detail, a higher mortality appeared to be present for HD patients at the start of treatment. This is possibly due to the fact that if dialysis had to be started in an acute setting, HD was used.

In the present study, a reduction of hospitalization for cardiovascular causes after starting dialysis was observed. This finding is consistent with earlier published studies [18–26]. In contrast, in our study, the number of hospitalization days for all causes did not change. Hospitalizations for non-cardiovascular causes appeared to be especially pronounced in patients who were already hospitalized at the start of dialysis and were in general not related to complications of the treatment. In the study performed by Rubin and Ball [27], all-cause hospitalization rates failed to improve due to dialysis complications and underlying heart disease.

After starting dialysis, the majority of the study population showed an improvement of the functional status during the follow-up period. Almost 62% increased two NYHA classes after starting PD, although in only two patients, an improvement of LVEF was observed. In our study, only 11 patients had a second echocardiography and six patients for all causes, was reduced. Thirdly, improvements in quality of life and functional status were observed after starting dialysis.

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After starting dialysis, the majority of the study population showed an improvement of the functional status during the follow-up period. Almost 62% increased two NYHA classes after 4 months of dialysis. This finding is also consistent with earlier studies [7, 22, 23, 25, 26]. Mehrotra and Kathuria [7] analysed seven studies and concluded that >90% of the patients improved in functional status after starting dialysis. In the study of Sánchez et al. [25], all patients improved one or two classes in functional status.

In the study of Kim et al. [11], all patients exhibited a functional improvement by one or two NYHA classes after starting PD, although in only two patients, an improvement of LVEF was observed. In our study, only 11 patients had a second echocardiography and six patients
showed an improvement of LVEF, but changes were not significant. The same held true for changes in NT-proBNP. Thus, it appears that the effect of increased fluid removal by extra-corporeal therapy has a significant effect on functional status, but likely not on cardiac function per se.

A reduction in hospitalization for cardiovascular causes and an improvement in functional status after starting dialysis in CRS Type 2 could consequently lead to an improvement in quality of life. Quality of life improved in 75% of the patients included in this study, whereas the scores on the Minnesota Living with Heart Failure Questionnaire declined, although differences on repeated measures ANOVA did just not reach significance. This finding is consistent with the study of Stegmayr et al. [16], where 16 patients with CHF and treated with PD all improved within 1 month in functional status and also in quality of life. In the study of Bertoli et al. [6], two CHF patients were treated with a single nocturnal exchange with icodextrin. After at least 12 months of treatment, an improvement in quality of life in both patients was observed. Sánchez et al. [25] treated 17 patients known with treatment-resistant CHF with PD. Quality of life was increased, which was positively correlated with a better functional status, less hospitalizations and higher survival rate.

Thus, the results of the present study and those of others suggest that extracorporeal treatment may lead to a significant improvement in quality of life. However, admittedly, in our study the follow-up time was relatively short, limited to 8 months. Moreover, the incidence of technical complications associated with the dialysis therapy was relatively high and far greater as compared to our 'standard' dialysis population. In some cases, this resulted in hospitalization. We hypothesize that this might be due to the fact that our study concerned a sick and relatively elderly population with multiple comorbidities, making the patients more prone to complications [28]. Notably, in contrast to hospitalizations for cardiovascular causes, the number of all-cause hospitalizations did not decrease significantly.

Diuresis decreased throughout the follow-up period, whereas mean GFR remained stable. In the study by Sánchez et al. [25], urine production did not change throughout the study period of 12 months. However, mean daily ultrafiltration was higher in our study, although our sample included patients on IHD.

In this prospective study, we could not detect any prognostic factors for survival in patients known with treatment-resistant CHF complicated by severe renal failure and starting dialysis. This is in contrast to the results of our retrospective study in which age and diabetes were poor prognostic factors for survival. We did not observe a significant effect of elementary baseline variables such as age, GFR, Charlson’s comorbidity index and LVEF on outcome nor a significant difference between PD and IHD in Cox regression analysis. However, we admit that the number of patients in our analysis is too small to draw firm conclusions on this subject.

Limitations of the present study are the limited number of patients, relative short follow-up time with regard to functional status and quality of life measurements and incomplete measurements with regard to cardiac function. Patients were treated with both PD and IHD. More prospective studies are needed in order to assess effect and outcome of dialysis in patients with treatment-resistant CHF.

Conclusions

In our opinion, based on the results in the literature and our own clinical experience, extracorporeal treatment is a feasible therapy in a selected group of patients with treatment-resistant CRS Type 2 complicated with severe renal insufficiency. After starting dialysis, a reduction in hospitalizations for cardiovascular causes was observed, but not in hospitalizations for all causes. The number of technical complications related to the dialysis therapy in this population was relatively high. In this study, we could not detect a prognostic factor for survival. Therefore, patient selection remains difficult. Further investigations are needed to better define the criteria for starting renal replacement therapy in treatment-resistant CHF.

Conflict of interest statement. None declared.

References

Serum phosphorus as a predictor of low-grade albuminuria in a general population without evidence of chronic kidney disease

Hajeong Lee¹, Se Won Oh², Nam Ju Heo³, Ho Jun Chin², Ki Young Na², Suhnggwon Kim¹ and Dong-Wan Chae²

¹Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, ²Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea and ³Department of Internal Medicine, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Korea

Correspondence and offprint requests to: Dong-Wan Chae; E-mail: cdw1302@snubh.org

Abstract

Background. High levels of serum phosphorus, even within the normal range, have been associated with cardiovascular (CV) morbidity. Low-grade albuminuria (LGA) was demonstrated to be related to increased CV events in various study populations. The present study aimed to investigate the association between serum phosphorus levels and LGA in the general population.

Methods. We examined the individuals who had undergone health inspections. We evaluated the correlation between serum phosphorus and LGA in 8953 participants (mean age, 47.4 years) with estimated glomerular filtration rates (eGFRs) ≥60 mL/min/1.73m² and urinary albumin-to-creatinine ratios (UACRs) <30 mg/g. Participants who underwent a colonoscopy were excluded.

Results. The mean UACR was significantly higher in the uppermost quartile group of serum phosphorus concentrations than in other quartile groups. In the multivariate regression analysis, serum phosphorus remained an independent predictor of increased UACR (B = 0.610, P < 0.001). Subgroup analyses showed that this association was maintained irrespective of age, gender, presence of hypertension or diabetes, body mass index and eGFR.

Conclusions. In our population-based study, higher serum phosphorus was independently related to LGA in individuals without evidence of renal dysfunction. Further investigations are warranted to clarify the precise mechanism of the association between serum phosphorus and LGA.

Keywords: serum phosphorus concentration; low-grade albuminuria; general population