

Case Report

Long-Term Prognosis of Patients Receiving Hemodialysis Therapy in Conjunction with Regular Continuous Ambulatory Peritoneal Dialysis

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Abstract

Background: We previously reported that once-a week hemodialysis (HD) therapy in conjunction with regular continuous ambulatory peritoneal dialysis (PD) improved solute clearance and symptoms related to uremia in PD patients. Here, we describe a long-term follow up on a large cohort of PD patients receiving combination therapy with PD and HD. We analyzed 105 patients (average age: 55.1±11.8 years old; F/M: 31/74; duration of PD: 32.2±27.8 months) who were receiving PD and suffered from insufficient dialysis dose (weekly creatinine clearance of less than 45 L/week). Once-a week HD therapy was introduced between 2000 and 2009. Patients were observed for 5 years. Demographic and comorbidity data were collected. The primary outcomes for the present study were technical failure and death. Secondary outcomes included the changes in parameters that influenced mortality of dialyzed patients. Cumulative rates for technical failure were 24 % at 3 years and 54% at 5 years after the initiation of add-on HD therapy. Survival rates were 92 and 89% after 3 and 5 years, respectively. Twelve patients died during the observation period. Three patients died from cardiovascular diseases and 5 patients died from infectious diseases during the observation period. Combination therapy produced reduction in both systolic and diastolic blood pressures, elevation of serum albumin, and significant improvement of erythropoietin resistance index compared with previous treatment of PD alone. This study provides evidence that add-on HD therapy in conjunction with regular PD is effective for PD patients who suffer from insufficient dialysis dose for a long-term.

Keywords: Capd; Hd; Weekly Creatinine Clearance; Albumin; Survival

Introduction

As renal replacement therapy, three modalities of transplantation, hemodialysis (HD) and peritoneal dialysis (PD) are available for patients with end-stage renal disease (ESRD). Recently however, patients with ESRD have hesitated to select PD as an initial modality of dialysis therapy. This is because over time, few PD patients stay on PD more than 5 years from initiation of therapy. It was also reported that a large proportion of dialysis patients transfer from PD to HD every year [1,2]. Among the factors for discontinuation of PD, peritoneal transport status which may be associated with adverse clinical outcome [3] is of utmost importance. In Japan, previously Kawaguchi et al. [4] reported that failure of ultrafiltration was the principal reason for withdrawal from PD. Moreover, the association between peritoneal transport status and weekly creatinine clearance is expected [5,6] Guidelines on targets for solute clearance have now emerged, and the most prominent one is the National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-DOQI) guidelines [7]. The NKF-DOQI targets a weekly creatinine clearance (WCC) of more than 60 L per 1.73 m². To achieve adequate weekly creatinine clearance, several procedures can be used. One way is by the use of automated PD (APD), although no decisive data are available for the effects of increasing prescriptions on patients outcomes. Since one HD session is equivalent to 2 to 3 days of PD in terms of creatinine clearance, the addition of HD to PD patients who do not achieve the WCC targets would be an alternate way [8,9] There are considerable obstacles to this approach that are almost entirely nonmedical, such as physician biases and conservative policies. Recently a number of studies in English have been reported [8,10-14] In spite of these reports, there are few demonstrations of a long term effect of combination therapy. In the present study, long term clinical outcomes of combination therapy will be presented.

Patients and Methods

One hundred and five patients who received HD once a week between 2000 and 2009 in the Kidney Disease Center in Saitama Medical University, SAITAMA Japan were analyzed. Informed consent was obtained before starting PD therapy. This study was performed in accordance with the principles of the World Medical Association Declaration of Helsinki and was conducted in the Kidney Disease Center in Saitama Medical University, SAITAMA Japan.

Patients who had less than 6 months of follow-up and had been on HD or received a kidney transplant before PD were excluded for analysis. All patients were under a standard regimen with 3 to 4 daily exchanges of 1.5 or 2 liters of dialysate. The criteria for introduction of HD as in combination therapy was determined as creatinine clearance of less than 45 L/week calculated by Adequest or as fluid overload.

For analysis of patients' survival and technical failure 5 years after the start of adding HD therapy, data for age, sex at the start of PD, underlying renal disease, comorbidities, follow-up duration, and causes of death and laboratory values were collected.

The causes of death were categorized as cardiovascular diseases (CVD) including stroke, malignancy, infection and others. Patients on PD were permanently transferred to HD due to inadequate dialysis, peritonitis, ultrafiltration failure, exit-site infection, tunnel infection, and mechanical or operational problems and then technical failure was defined as transfer to HD or renal transplantation.

Regular Treatment Modality in the Kidney Center in Saitama Medical University

More than 60% of patients were treated with a standard PD regimen that consisted of 3 to 4 daily exchanges of 1.5 or 2 liters of dialysate, while other patients used 1 to 2 daily exchanges of dialysate. The strength of the bags was individualized to maintain the desired weight. Dwell times were also individualized to maximize overall ultrafiltration volumes. Mean daily dietary intake was recorded from individual 24-hour food records during a three-day period at the start of the study. All subjects consumed between 0.8 and 1.0 g of protein/kg/day and their energy intake exceeded 25 kcal/kg/day and salt intake was restricted to less than 9 g daily throughout the study.

Combination of PD and HD

A 4 hr HD was added once a week after 6 consecutive days of PD. On the morning of HD, the PD dialysate was drained before HD. HD was carried out using a bicarbonate dialysate and a dialyzer with a polysulfone dialysis membrane.

Patient Monitoring

Patients were followed every month during the study period. At each clinic visit, serum creatinine, electrolyte concentrations, complete blood count, and other serum

chemistries (uric acid, glucose, and liver enzymes) were measured. Indices of the adequacy of dialysis, including weekly CCR, were calculated using the Adequest computer program, version 2.0 (Baxter Healthcare, Tokyo, Japan) for Windows. Chest radiographs were obtained regularly, and cardiothoracic index was calculated according to established methods.

During the study, target home blood pressure (BP) was 130/80 mm Hg or lower and home BP measurements were encouraged. The selection of an antihypertensive agent depended on the physicians preference. Subjects were treated with recombinant human erythropoietin (rHuEPO) as necessary and their hemoglobin levels were maintained between 10 to 11 g/dL. Subjects were given oral iron supplementation if they were diagnosed with iron deficiency.

Subjects with parathyroid hormone levels greater than 500 pg/ml were treated with 1,25(OH)₂D₃ and CaCO₃ supplements, while patients with levels lower than 70 pg/ml were treated with CaCO₃ to reduce the degree of hyperphosphatemia. Doses were adjusted based on serum levels of calcium and phosphate. Lipid lowering drugs, primarily statin derivatives, were administered if serum low density lipid cholesterol levels exceeded 140 mg/dl.

Erythropoietin resistance index (ERI) was calculated as the weekly weight-adjusted dose of EPO divided by the hemoglobin level.

Statistical Analysis

Results are expressed as mean ± standard error of the mean.

The comparisons of before and after addition of HD therapy were made with one-way analysis of variance with repeated measurement followed by Bonferroni's test. Technical failure and patients survival rates were determined using the Kaplan-Meier method. Statistical significance was set at $p < 0.05$.

Results

Baseline Characteristics of all participants

Table 1 shows the baseline characteristics at the start of HD for all PD patients. A total of 105 were analyzed in our study with an average age of 55.1±11.8 years; (female/male: 31/74; duration of PD: 32.2±27.8 months). Chronic glomerulonephritis, diabetes mellitus and hypertension accounted for the three most common causes of ESRD.

Table 1 Characteristics of Patients

Number of Patients (female/male)	105 (31/74)
Age (years)	55.1 ± 11.8
Duration of PD (months)	32.2 ± 27.8
Underlying disease (%)	
Chronic glomerular disease	47 (45)
Diabetic nephropathy	27 (26)
Nephrosclerosis	9 (8)
Others	22 (21)

Number and (%)

Reasons for addition of HD

In Table 2, the reasons for PD patients utilizing HD are shown. Failures of solute and volume removal, i.e., inadequate dialysis, were the 2 major reasons. Besides, physicians' preferences were also important for addition of HD for PD patients.

Table 2 Reasons of add-on therapy

Uremia	50(49%)
Overhydration	27(26%)
dementia	2(2%)
Blood mixed into waste fluid	1(1%)
Physicians' preference	22(22%)

Number and (%)

Causes of Death

Table 3 shows the classification of the causes of death of patients. Infection was the leading cause of death followed by CVD.

Table 3 Causes of death

Causes	
Infection	5(41%)
Cardiovascular diseases	3(25%)
Cerebrovascular diseases	2(17%)
Malignant tumor	2(17%)

Number and (%)

The reasons for discontinuation of treatment with HD and PD in combination are shown in Table 4. Death was the leading cause of discontinuation followed by peritonitis and long-term PD therapy.

Table 4 Reasons for discontinuation of treatment with HD and PD in combination

death	12(23%)
Peritonitis relating PD	9(18%)
Long-term PD	9(18%)
Home hemodialysis	6(11%)
uremia	3(6%)
overhydration	3(6%)
dementia	3(6%)
Suspicious of sclerosing Encapsulating Peritonitis	2(4%)
Perforation of intestine	1(2%)
Post AVR operation	1(2%)
Kidney transplantation	1(2%)
No availability of assistant	1(2%)

Outcome

Technical Failure

Except for death, peritonitis, a long term PD treatment, and transfer to home HD were 3 reasons for discontinuation of combination therapy. Kaplan-Meier technical failure curves are shown in figure 1. Cumulative technical failure rates at 3 and 5 years were 24% and 54% respectively. (Figure 1)

Kaplan-Meier Curve

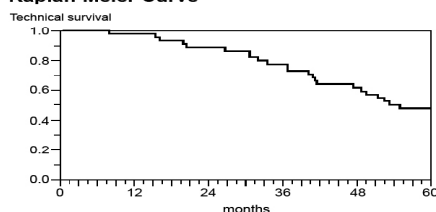


Fig. 1

Figure 1. Kaplan-Meier technical failure curve. Technical failure rates at 3 and 5 years were 24% and 54% respectively.

Patients Survival

Kaplan-Meier survival curves for patients are shown in figure 2. Patients' survival rates at 3 and 5 years were 92% and 89% respectively. (Figure 2)

Kaplan-Meier Curve

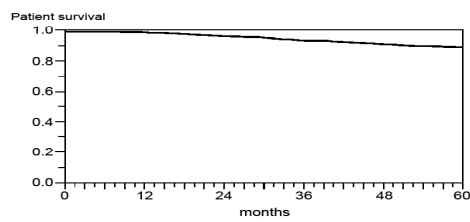


Fig. 2

Figure 2. Kaplan-Meier patient's survival curves

Cumulative proportional patient survivals at 3 and 5 years were 92% and 89%.

Effects of Add-On HD Therapy on SBP and DBP

There were reductions in both SBP (140 ± 3 mm Hg vs. 135 ± 5 mm Hg) and DBP (81 ± 2 mm Hg vs. 71 ± 3 mm Hg) at 3 years. (P<0.05) (Figures 3 and 4)

Changes in systolic blood pressure

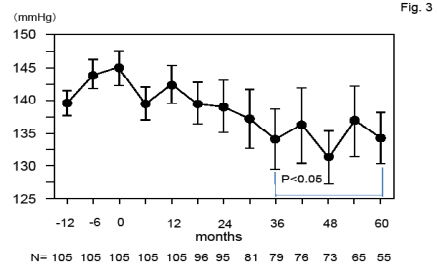


Fig. 3

Figures 3 and 4. Changes in systolic (SBP) and diastolic (DBP) blood pressures

SBP gradually decreased with values reaching statistical significance at year 3 and were maintained at less than 140mm Hg until the end of the year 5 (p<0.05). DBP also decreased with similar pattern of changes in SBP. (P<0.05)

Changes in diastolic blood pressure

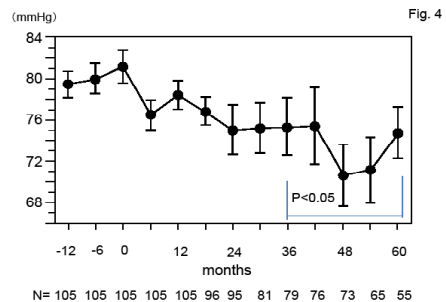


Fig. 4

Figures 3 and 4. Changes in systolic (SBP) and diastolic (DBP) blood pressures.

Effects of Add-On HD Therapy on Urine Volume

Urine volume decreased during the first year and was maintained during the next 2 years. At year 4, there was no urine volume to record. (Figure 5)

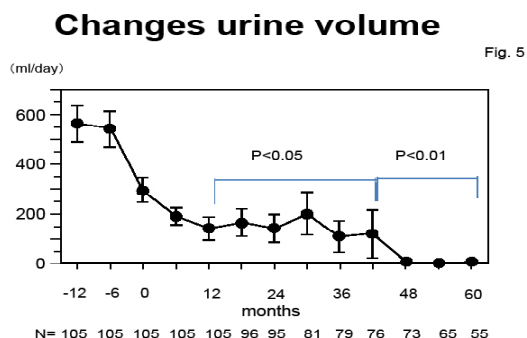


Figure 5. Changes in urine volume.

Urine volume was abruptly decreased during the first year after the add-on HD therapy and was maintained during the next 2 years. At 4 years after add-on HD therapy urine volume became zero.

Effects of Add-On HD Therapy on Serum Albumin

The level of serum albumin increased from 3.2 ± 0.1 at the baseline to 3.4 ± 0.1 mg/dL at 2 ½ years and was maintained during the rest of observation period at the levels of 3.0 mg/dL. (P<0.05) (Figure 6)

Changes in serum albumin

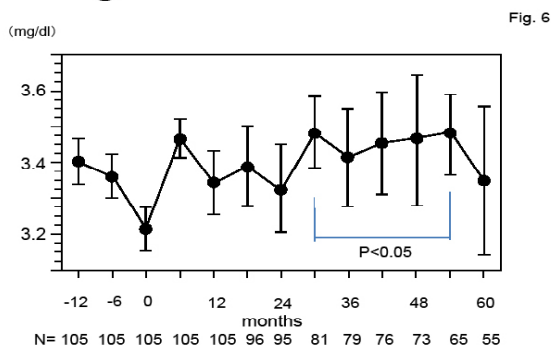


Figure 6. Changes in serum albumin.

Serum albumin was significantly reduced from 3.4 ± 0.1 at the baseline to 3.4 ± 0.1 mg/dL at 2 1/2 years and was maintained during the rest of the observation period at the levels of 3.0 md/dL. (P<0.05)

Effects of Add-On HD Therapy on Serum Creatinine

The levels of serum creatinine decreased from 12.5 ± 0.9 to 11.5 ± 1.0 mg/dl but without significance during the observation period (P=0.15). (Figure 7)

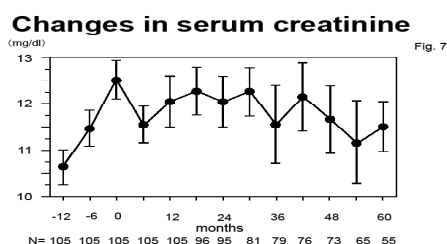


Figure 7. Changes in serum creatinine.

Serum creatinine was decreased from 12.5 ± 0.9 to 11.5 ± 0.6 mg/dL at year 3 without significance.

Effects of Add-On HD Therapy on Hemoglobin

The levels of hemoglobin were increased from 8.9 ± 0.1 to 10.3 ± 0.2 g/dL at year 3 year after the start of addition of HD and then increased toward the end of the observation period. (P<0.05) (Figure 8)

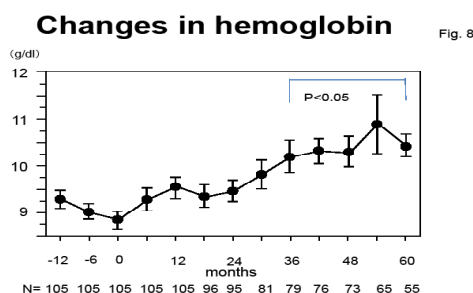


Figure 8. Changes in Hemoglobin.

Hemoglobin was increased from 8.9 ± 0.1 to 10.2 ± 0.2 g/dL at the end of 2 years and then further increase toward the end of the observation period. (P<0.05)

Effects of Add-On HD Therapy on Dose of rHuEPO

Before the start of add-on HD therapy, the average required dose of rHuEPO was 5500 ± 600 IU per month. However, since hemoglobin levels increased gradually in response to our treatment regimen, subjects required reduced doses of rHuEPO ($5000 + 600$ IU per month).

Effects of Add-On HD Therapy on ERI

ERI was reduced from the start of addition of HD and reached significance at year 3 (9.8 ± 0.5 vs. 9.0 ± 1.0 U/kg/week/g per 100 ml; P<0.05). (Figure 9)

Erythropoietin resistance Index

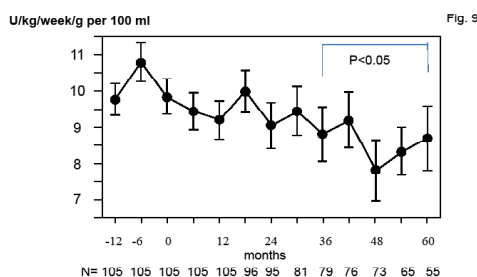


Figure 9. Changes in ERI.

ERI was reduced from the start of edition of HD and reached statistical significance at year 3. (P<0.05)

Effects of Add-On HD Therapy on Calcium and Phosphate Metabolism

There were no significant changes in serum levels of calcium and phosphate and parathyroid hormone.

Antihypertensive Medication

According to reductions of blood pressures after the start of add-on HD therapy, the number and types of antihypertensive treatment regimen were changed.

Discussion

This study showed that combination therapy with HD and PD is feasible as renal replacement therapy (RRT) in long-term PD patients. Previously, Kawanishi et al. [15] proposed that combination therapy should be used in PD patients showing insufficient solute clearance and improved clinical parameters. In the present study, all patients had insufficient dialysis in solute and volume removal, indicating that all patients were underdialyzed based on the new Kidney Disease Outcomes Quality Initiative guidelines (K/DOQI 2006) [16]. The present data clearly showed that mild underdialysis by PD could be salvaged by once-a week HD independently by timing the initiation of combination therapy. In a study of the long-term effects of combination therapy conducted in our hospital, both drain volume and creatinine clearance increased significantly. This clearly supports the hypothesis by Kawanishi et al. [15] that combination therapy with HD and PD improves clinical status in patients in whom adequate solute and fluid removal is difficult to achieve with PD alone. Moreover, despite a progressive loss of residual renal function observed in the study of effects of early start of combination therapy, solute clearance in these patients was relatively well maintained. These clinical findings were well in accord with Szeto's proposal that the cut-off values of a weekly creatinine clearance were more than 50 L but less than 60 L [17]. Maiorca et al. [18] found that patient fatigue and psychosocial factors accounted for about half of the total number that changed to HD in long-term PD patients. This may in part be related to lower solute clearance. The use of add-on HD therapy may be advantageous in some of these patients when patients are relatively underdialyzed.

Patient survival has been reported to be low in PD patients [19]. However, some reports from Korea (20), Hong Kong [21] and Japan [22] demonstrated a relatively higher survival rate compared with those from Europe [2] and USA. In the present study, the survival rate was significantly higher than reported in Japanese patients [22].

Previously Han et al. [20] reported the technical failure at 5 years was more than 70% since 1993. The average age of the patients was younger than those in our present study. The latter were 60 years and the former was 56 years. However, in the present study, the proportions of diabetic patients were lower than those reported from Asian countries, where more than 30 % of diabetic patients were recruited. This might cancel the favorable findings in the study of Han et al. [20], because it has been reported that diabetic patients on PD had shorter

Setting aside these factors, the definite difference between the reports from Korea and Hong Kong and the present study lies in the method for continuation of PD therapy. In general, the decreasing ability of the peritoneal membrane for ultrafiltration is compensated by increases in frequency of changing bags and/or in volume of bags, which eventually lead to PD failure within 10 years.

In the present study, instead of applying these methods, addition of once a week HD was tried to compensate for inadequate dialysis and volume removal. In the present study, residual urine volume of the PD patients decreased abruptly 12 months before starting complementary HD, suggesting that those patients were both insufficient for ultrafiltration and overhydration.

According to the statistics of causes of death in Japanese HD patients in 2004, the leading cause of death was cardiac failure (27.7%) followed by infectious disease (18.5%). In the present study, the percentage of the causes of death due to CVD (25.0 %) and infection was 41%, reflecting the causes of death mainly due to PD therapy, in which infection due to peritonitis is the main cause of death.

In the study of the long-term effects of combination therapy, in addition to solute clearance, combination therapy with HD and PD increased serum albumin level, hemoglobin concentration, drain volume, and decreased SBP and DBP. It is well known that serum albumin correlates with morbidity and mortality in PD as well as in HD patients [23-25]. The practical significance of this correlation remains unclear, though it is likely that low serum albumin is a marker rather than a direct cause of this morbidity, and which may be the result of malnutrition. In the study of effects of early start of combination therapy, all patients had well maintained solute clearance in spite of gradual diminished residual renal function, indicating that early start of combination therapy might be one of the benefits for patients new to ESRD. This finding concurs with the early reports by McIntyre [26].

Maintenance of high blood pressure is known to cause CVD in patients receiving either PD or HD. In the present study, blood pressure tended to fall without any further addition of antihypertensive agents, indicating that some substances related with elevation of blood pressure were removed in dialyzed patients [27]. As shown in our previous studies, combination therapy adequately removed both volume and solute and contributed to reduction of blood pressure.

Lastly, anemia was markedly improved with reduced erythropoietin resistance index, contributing to improvement of technical failure and prolongation of survival [28,29].

Limitations of Our Study

There are some limitations in the present study. First, it was a single-center study and thus center specific effects cannot be excluded. Second, selection bias in addition of HD to PD might have influenced the results. Third, there were no definitions for withdrawal from HD and PD in

combination therapy. Despite those limitations, this study proposes a new strategy for PD first therapy [30,31].

In conclusion, the present study demonstrated that PD and HD in combination produced longer patient survival and reduced the technical failure associated with PD alone. This Manuscript is dedicated to Dr.H. Hosi, who passed away before completion of his work.

Conflict of interest

The authors declare that they have no conflicts of interest in this study.

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Mrs Sachiko Nakazato, a secretary, calculated the data and typed the manuscript.

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