Long-Term Survival Benefits of Combined Hemodialysis and Peritoneal Dialysis

Recently, it was reported that concomitant hemodialysis (HD) in peritoneal dialysis (PD) patients facilitated continuation of PD treatment and mitigated the deterioration of peritoneal function in patients with uremic symptoms and excess body fluid associated with loss of residual renal function.

To determine the effect of combined HD and PD on patient and technique survival, we undertook a retrospective cohort study of patients who underwent PD at Saitama Medical University Hospital between 1995 and 2010. We compared patients who started PD during 1995 – 2002 with those who started during 2003 – 2010. Because our center started a new strategy of supplementing PD with once-weekly HD in 2000, the effects of combination therapy could be determined by comparing the data obtained during the two periods.

The 440 patients (274 men, 166 women) who started PD during the study period had a mean age of 60.2 ± 7.3 years. The mean age was significantly higher in the 2003 – 2010 group than in the 1995 – 2002 group. Using a Kaplan–Meier plot, we observed a significant difference in technique survival (p < 0.001). The technique survival rate at 3 and 5 years was, respectively, 89% and 74% in the 2003 – 2010 group and 68% and 33% in the 1995 – 2002 group (p < 0.05). Cumulative patient survival at 3 and 5 years was, respectively, 87% and 72% in the 2003 – 2010 group and 69% and 51% in the 1995 – 2003 group (p < 0.01).

Patient and technique survival were significantly improved in PD patients receiving the combination of HD and PD.

Key words
Hemodialysis, combination therapy, technique survival, patient survival

Introduction
It is well known that few peritoneal dialysis (PD) patients stay on PD more than 5 years from initiation of therapy. It is also known that a large proportion of dialysis patients transfer from PD to hemodialysis (HD) every year (1,2). Peritonitis recurrence and inadequate dialysis are considered the two major causes of transfer. Jaar et al. (3) reported that, of 292 PD patients followed prospectively, 40% switched within 1 year and 70% within 2 years of starting PD. In their series, the most common reasons for the switch were infection (36.9%) and volume overload (18.5%). In Japan, Kawaguchi et al. (4) reported that, in 224 patients, overall survival was 50% at a mean of 5.5 years, and ultrafiltration failure was the most frequent reason for withdrawal from PD.

Several methods have been proposed for the prevention of ultrafiltration failure, including use of icodextrin and inhibition of the renin–angiotensin system (5). Recently, Moriishi et al. (6) suggested that concomitant HD facilitates continuation of PD treatment and retention of peritoneal function in patients with uremic symptoms and excess body fluid associated with a loss of residual renal function. Because our center started a new strategy of supplementing PD with once-weekly HD in 2000 (7,8), we evaluated the effects of combination therapy by comparing the patient data obtained during the periods before and after that change.

Methods
We recruited 440 patients attending the Kidney Disease Center in Saitama Medical University Hospital, Saitama, Japan, who started PD from 1995 to 2010. Patients with less than 6 months of follow-up and those who had been on HD or who had received a
kidney graft before PD were excluded from the analysis. The criterion for introducing HD in combination therapy was a weekly creatinine clearance of less than 45 L [calculated using PD Adequest (Baxter Healthcare, Tokyo, Japan)] or fluid overload (8).

To analyze patient and technique survival during the 14-year period, we collected such patient data as age at the start of PD, sex, underlying renal disease, comorbidities, follow-up duration, cause of death, and the occurrence of insufficiency or technique failure (that is, inadequate dialysis, peritonitis, ultrafiltration failure, exit-site infection, tunnel infection, and mechanical or operational problems). Causes of death were categorized as cardiovascular, stroke, malignancy, infection, and others. Technique failure resulted in transfer to HD or renal transplantation.

Informed consent was obtained from the patients before PD start. The present study was performed in accordance with the principles of the Declaration of Helsinki.

Regular treatment modality
More than 60% of the patients were treated with a standard PD regimen of 3 – 4 daily exchanges of 1.5 L or 2 L of dialysate. Other patients used 1 – 2 daily exchanges. The solution concentration 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 3-day period at the start of the study. All subjects consumed between 0.8 g and 1.0 g of protein per kilogram body weight daily, and their daily energy intake exceeded 25 kcal per kilogram body weight. Salt intake was restricted to less than 9 g daily throughout the study.

Combination of PD and HD
A 4-hour HD session was added once weekly after 6 consecutive days of PD. On the morning of HD, the PD dialysate was drained before the HD session. Bicarbonate dialysate and a dialyzer with a polysulfone dialysis membrane was used for HD.

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, liver enzymes) were measured. Indices of the adequacy of dialysis, including weekly creatinine clearance, were calculated using the PD Adequest software for Windows (version 2.0). Chest radiographs were obtained regularly, and cardiothoracic index was calculated using established methods.

During the study, target home blood pressure was 130/80 mmHg or lower, and home blood pressure measurements were encouraged. The selection of antihypertensive agents depended on physician preference. Subjects were treated with recombinant human erythropoietin as necessary, and hemoglobin levels were maintained in the range 10 – 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)_{2}D_{3} and CaCO_{3} supplements, and patients with levels lower than 70 pg/mL were treated with CaCO_{3} 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 cholesterol exceeded 240 mg/dL.

Statistical analysis
Results are expressed as mean ± standard error of the mean. Statistical analyses used the Student t-test for unpaired samples and the Mann–Whitney test to compare means. Statistical significance was set at \( p < 0.05 \). The analyses were performed using the JMP software application (version 9: SAS Institute, Cary, NC, U.S.A.).

Patient and technique survival rates were determined using the Kaplan–Meier method. A log-rank test was used to compare patient and technique survival between groups.

Results
Baseline characteristics of the study subjects
Table I shows baseline characteristics for all patients at the start of PD. The 440 patients analyzed in the study had a mean age of 60.2 years, and 62.6% were men. Chronic glomerulonephritis, diabetes mellitus, and hypertension were the three most common causes of end-stage renal disease. Mean age was significantly higher in the 2003 – 2010 group than in the 1995 – 2002
group \((p < 0.05)\). Diabetic patients constituted a larger proportion of the 1995 – 2002 group than of the 2003 – 2010 group, but that difference was nonsignificant.

Table II shows the ages of the patients by underlying disease. The mean age of patients with glomerulonephritis was greater in the 2003 – 2010 group than in the 1995 – 2002 group, but nonsignificantly so. Differences in age for patients with the other two underlying diseases were also nonsignificant.

**Causes of death**

Table III shows the cause-of-death classifications for the patients. In a nationwide survey of Japanese patients on HD, cardiac and infectious disease were the two major causes of death. In the present study, the two groups showed no significant difference in the proportion of infectious disease, but more patients in the 2003 – 2010 group had cardiovascular diseases. That finding might reflect the aging process, because the patients in the 2003 – 2010 group were also older than those in the 1995 – 2002 group.

**Transfers directly to HD or to combination HD and PD**

All patients started PD as their initial dialysis therapy. Thereafter, some patients switched directly from PD to HD; others needed HD as a complementary therapy (Table IV). In the 2003 – 2010 group, 44% of the patients used combination therapy as their second dialysis modality, a proportion that was significantly higher than the 14% of patients in the 1995 – 2002 group who used combined PD and HD.

**Outcomes**

**Technique survival**

Figure 1 shows Kaplan–Meier technique survival curves for the patients. Technique survival was significantly different between the groups \((p < 0.001)\). The technique survival rate at 3 and 5 years was 89% and 74% in the 2003 – 2010 group and 68% and 35% in the 1995 – 2002 group.

**Patient survival**

Figure 2 shows that the duration of patient survival was significantly shorter in the 1995 – 2003 group than in the 2003 – 2010 group (Kaplan–Meier analysis, \(p < 0.01\)). The cumulative patient survival rates at 3 and 5 years were 87% and 72% in the 2003 – 2010 group and 69% and 51% in the 1995 – 2003 group.

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**Table I**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
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<tbody>
<tr>
<td>--------------------------------</td>
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<tr>
<td>Patients ((n))</td>
<td>440</td>
</tr>
<tr>
<td>Sex ((n\ men/women))</td>
<td>274/166</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>60.2±7.3</td>
</tr>
<tr>
<td>Underlying disease ([n\ (%)])</td>
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<tr>
<td>Glomerulonephritis</td>
<td>308 (70)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>83 (19)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (8)</td>
</tr>
<tr>
<td>Others and unknown</td>
<td>11 (3)</td>
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</tbody>
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**Table II**

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<tr>
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<tbody>
<tr>
<td>Glomerulonephritis</td>
<td></td>
<td>59.3±9.4</td>
<td>55.7±13.9</td>
<td>63.3±12.1</td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>63.5±10.6</td>
<td>62.6±11.0</td>
<td>65.9±12.1</td>
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<tr>
<td>Hypertension</td>
<td></td>
<td>65.3±12.2</td>
<td>64.9±11.0</td>
<td>68.1±14.8</td>
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**Table III**

<table>
<thead>
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<th>Causes</th>
<th>Treatment group</th>
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<tr>
<td>Deaths overall ((n))</td>
<td>203</td>
</tr>
<tr>
<td>Deaths from ([n\ (%)])</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>41 (20)</td>
</tr>
<tr>
<td>Infection</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Stroke</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>109 (54)</td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease.

**Table IV**

<table>
<thead>
<tr>
<th>Transfer modality</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients ((n))</td>
<td>440</td>
</tr>
<tr>
<td>Patients transferring to ([n\ (%)])</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>124 (28)</td>
</tr>
<tr>
<td>Combination PD+HD</td>
<td>129 (29)</td>
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</tbody>
</table>

\(a\ p < 0.05.\)

\(b\ p < 0.01.\)
Discussion

In this longitudinal cohort study, 440 incident PD patients were recruited from a single center. The results showed that the mean age of patients treated during 2003 – 2010 was significantly higher than that of patients treated during 1995 – 2002. In spite of advancing age, patient and technique survival were both significantly higher in patients who started PD after 2003 than in those who started before 2002.

Patient survival has been reported to be low in PD patients (9). However, compared with reports from Europe (2) and the United States, some reports from Korea (10), Hong Kong (11), and Japan (12) have demonstrated a relatively higher survival rate. In the present study, the survival rate for the 1995 – 2002 group was equivalent to that seen in data from Japan (12). However, the survival rate was significantly higher for the 2003 – 2010 group than for the 1995 – 2002 group.

Previously, Han et al. (10) reported a better than 70% technique survival at 5 years in the period since 1993 for patients whose average age was 56 (younger than the mean of 60 years in the present study). However, in our study, the proportion of patients with diabetes was lower than that reported from Asian countries, where diabetic patients typically constitute more than 30% of the PD population. That difference might negate the favorable findings in our study, because it has been reported that diabetic patients on PD experience shorter survival (11).

The foregoing factors aside, the chief difference between the reports from Korea and Hong Kong and the present study is the method for continuation of PD therapy. In general, compensation for the declining ultrafiltration ability of the peritoneal membrane is attained by increasing the frequency of exchanges or the volume of dialysate; however, PD failure still typically occurs within 10 years. In the present study, instead of applying those methods, once-weekly HD was added to try to compensate for inadequate dialysis and volume removal. When weekly ultrafiltration began to decline below 45 L as calculated by PD Adequest, once-weekly HD in combination with PD was recommended to the patients (7,8). Recently, Kawanishi and McIntyre (13) and Kawanishi and Moriishi (14) reported that, compared with PD alone, complementary dialysis therapy provided higher weekly clearances and longer patient survival. Our earlier studies also reached similar findings, in that weekly clearance increased after addition of once-weekly HD (7,8). The results of the present study extend the data presented by Kawanishi and colleagues, providing further validation of adding combination therapy with HD to prolong PD.

Statistics on causes of death in Japanese HD patients in 2004 show that the leading cause was cardiac failure (27.7%), followed by infectious disease (18.5%). In the present study, significantly
more deaths from cardiovascular disease were observed in the 2003 – 2010 group (30.0%) than in the 1995 – 2002 group, but no difference in deaths from infectious disease was observed. That finding is probably attributable to the effects of advancing age. Also, despite there being no difference between the groups in the proportion of deaths from infection, the number of patients increased—possibly reflecting an increase in the number of patients undergoing combination therapy.

Limitations of the study
The present study has some limitations. First, it was a single-center study, and consequently, center-specific effects cannot be excluded. Second, selection bias resulting from the choice to switch from PD to HD or to add HD to PD might have influenced the results. Third, there was no definition for withdrawal from combination therapy with HD and PD. Fourth, the study compares data obtained during different time periods, which means that staff, methods, and procedures would have been different. Despite those limitations, our study proposes a new strategy for “PD First” therapy (15,16)

Conclusions
The present study demonstrates that, compared with PD alone, the combination of PD and HD resulted in longer patient and technique survival.

Disclosures
The authors have no financial conflicts of interest.

References

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