COMBINATION THERAPY WITH PERITONEAL DIALYSIS AND HEMODIALYSIS

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The greatest benefit of peritoneal dialysis (PD) is the continuous nature of the therapy, which results in steady-state levels of electrolytes as well as fluid and acid–base balance. A continuous sodium removal reduces water intake and makes appropriate fluid management possible, even if the ultrafiltration (UF) volume is small. Peritoneal dialysis is also beneficial in maintaining residual renal function (RRF) (1,2), which is known to be a determinant of patient survival (3). Therefore, PD can easily deliver effective dialysis treatment that maintains the life of end-stage renal failure patients. Even though successful outcomes for PD in anuric patients have been reported (4), standard PD may not be sufficient to avoid the risk of uremic complications when RRF declines (5–7). Increasing the dose of dialysis, currently the only measure available to diminish these risks, has the potential to increase the negative impact of the dialysis solution. An alternative to increasing the dose of PD is to combine PD with hemodialysis (HD). Despite only limited outcome data being available, such a combined therapy has rapidly gained popularity in Japan. It is expected that, in 2002, approximately 5.5% of PD patients were prescribed PD + HD (8).

McIntyre recently reported the results of a prospective study of such a combination therapy, PD + HD, referred to as bimodal dialysis, in 8 patients commencing dialysis (9). The objective of this combined therapy was to maximize solute removal and volume control. Patients were followed for at least 1 year. Their prescription consisted of highly efficient HD with a polysulfone membrane for 3 hours, at a dialysate flow rate of 750 mL/minute, twice weekly, without UF, and low-dose daily PD with two exchanges of 2 L conventional solution and/or icodextrin-based dialysate to optimize water removal. In short, their dialysis prescriptions aimed to achieve solute clearance by PD and HD, and continuous water removal, thereby maintaining RRF. McIntyre reported good hemodynamic/volume control, reduced need for antihypertensive medication, and unchanged RRF. It is well known that RRF declines rapidly during conventional HD treatment (10,11). One of the reasons for this is thought to be the intermittent nature of HD resulting in rapid changes in patients’ fluid status, suggesting that HD without UF could maintain RRF. The bimodal dialysis method proposed by McIntyre is noteworthy in that it corrects this disadvantage of HD. However, this particular advantage is of no benefit once RRF is lost.

In Japan, combination therapy with weekly HD started in 1995 (8,12). Later, limited experiences with combination therapy have also been reported from the United States (13). The primary difference compared to the McIntyre study is that, in Japan, the focus has been to use PD + HD in prevalent patients in whom RRF has decreased to the extent that management with conventional PD prescriptions is difficult. Thus, the combination regimen is used as an alternative to increasing the dose of PD. Also underlying this approach are the facts that, after loss of RRF, no matter how large a volume of PD fluid is used, removal of large molecular weight substances will become inadequate, resulting in, for example, an increase in β₂-microglobulin, leading to dialysis amyloidosis (14), and that an increase in the daily volume of PD fluid would accelerate deterioration of the peritoneal membrane, and thereby likely increase the risk of developing encapsulating perito-
neal sclerosis. The rationale for the latter hypothesis is that using large volumes means increasing exposure to glucose, which has been argued to constitute one of the main risk factors for encapsulating peritoneal sclerosis (15).

When patients have lost their RRF and management by PD alone becomes difficult, transfer to conventional HD has been the common practice in Japan. However, this eliminates the advantage of continuous treatment, which is the greatest benefit of PD apart from the maintenance of RRF.

We describe here the experience of using combination therapy in clinical practice in four centers in Japan between December 1995 and November 2002. Demographic data of the 52 included patients are given in Table 1. It should be pointed out that the presented data represent outcome of an analysis of retrospectively collected data. The aim of the study was to describe the indications for using combination therapy in Japan and its clinical outcomes.

The average duration of preceding PD was approximately 3.5 years. Average urine volume in 16 patients was 438 ± 225 (SD) mL/24 hours; the 36 remaining patients were anuric (urine volume ≤100 mL/24 hours). The clinical indications for initiating combination therapy were uremic symptoms related to insufficient small solute clearance (as judged by the prescribing physician) despite efforts to increase the dose of PD; fluid overload (including not only patients with UF failure, but also those with excessive body fluid for any reason); presence of hernia or hydrothorax that prevented an increase in dialysate volume; and PD holiday. The latter refers to a state of severe mental stress due to daily PD. The initial schedule of combination therapy was 5 or 6 days of PD and 1 weekly session of HD of 3 to 4 hours. If sufficient improvement did not occur on this regimen, the number of HD sessions was increased to 2 per week. The peritoneal dialysate was drained during the morning of a day with HD, and PD was reinitiated in the morning of the next or the second day after HD. All patients received HD at a dialysis center. The duration of PD at the start of the combination therapy was 43.2 ± 35.9 (mean ± SD) months, and the duration of combination therapy was 24.5 ± 17.7 months. The frequency of HD was increased to twice weekly in 21 patients 16.5 ± 15.2 months after the start of combination therapy. Twice-weekly HD was applied in 7 of the 16 patients for whom the combination therapy was continued for 24 months or more. All patients received PD as continuous ambulatory peritoneal dialysis (CAPD) using only glucose-based solutions. Hemodialysis was performed using bicarbonate dialysate and dialyzers with high permeability membranes. Overall, body weight, systolic blood pressure, and 24-hour urine volume decreased significantly (Table 2). The average 24-hour UF volume increased, although this improvement only reached statistical significance at 12 months. Moreover, serum creatinine declined (p < 0.05 at 6 months) and BUN and serum phosphate levels showed only minor fluctuations throughout the study. Overall, serum β2-microglobulin level was not influenced by the addition of HD, although the level decreased significantly in patients undergoing HD twice weekly (data not shown). Serum albumin level increased from 3.3 to 3.5 g/dL (p < 0.05) by month 6.

Changes in clinical signs and symptoms with once-weekly HD are given in Table 3. Before the start of combination therapy, indicators of inadequate dialysis, such as anorexia, skin pigmentation, peripheral neuritis, restless legs, and anemia, were observed in 14% – 29% of the patients. After 3 months, significantly fewer patients experienced anorexia, restless legs, anemia, and edema.

<table>
<thead>
<tr>
<th>TABLE 1Patients’ Demographic Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Gender (male/female)</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>PD duration before combination therapy</td>
</tr>
<tr>
<td>Duration of combination therapy</td>
</tr>
<tr>
<td>Type of kidney disease</td>
</tr>
<tr>
<td>Indication for combination therapy</td>
</tr>
<tr>
<td>Symptomatic, insufficient, small solute clearance</td>
</tr>
<tr>
<td>Fluid overload</td>
</tr>
<tr>
<td>Both</td>
</tr>
<tr>
<td>Contraindications to increase PD dialysis dose</td>
</tr>
<tr>
<td>PD holiday†</td>
</tr>
</tbody>
</table>
| PD = peritoneal dialysis; CGN = chronic glomerulonephritis; DN = diabetic nephropathy; NS = nephrosclerosis; PN = chronic pyelonephritis.
| *See text.* | Data are presented as number or mean±SD and (range). |
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KAWANISHI et al.

MARCH 2006 – VOL. 26, NO. 2

When PD is combined with HD, the dialysis dose by weekly HD must be converted to a continuous treatment value to obtain the total dialysis dose. The equivalent renal urea clearance (EKR; mL/minute) proposed by Casino and Lopez (16) was used as the conversion method. The calculated HD dose was added to the dialysis dose achieved by PD 5–6 days per week to obtain the total weekly dialysis dose for evaluation (12).

The total (PD + RRF) weekly Kt/V at the beginning of combination therapy was 1.86 ± 0.52. After 3 months of combination therapy, total weekly Kt/V (PD + RRF + HD) was 2.21 ± 0.25. It should, however, be pointed out that, up to now, no data exist that allow direct extrapolation of such combined Kt/V data to numerical criteria for “adequate” dialysis, as established by outcome trials in single modality use. Nevertheless, uremia-related symptoms, especially anorexia and restless legs, improved (Table 3). In addition, epoetin-resistant anemia improved significantly. The increase in serum albumin may have been associated with either reduced effluent losses of proteins and/or an improvement in nutrition related to the improvement in anorexia. The latter explanation is supported by an increase in serum phosphate (Table 2), which suggests an increase in protein intake.

It is well known that it is difficult to achieve adequate UF with PD when RRF declines, especially if avoiding the use of more hypertonic solutions that are known to negatively impact membrane function (17). Combination therapy was initiated because of fluid overload in 26 (50%) of the 52 patients and resulted in improvement in edema and significantly decreased blood pressure.

It is of interest to note that the average 24-hour PD UF volume remained unchanged for 24 months. It may be speculated that the intermittent peritoneal rest during days with HD may have induced a change in peritoneal permeability (18). Moreover, in this study, 24-hour urine volume declined over the 2-year study period, indicating that this mode of combination therapy in the present study population did not preserve RRF.

### TABLE 2

Changes in Clinical and Biochemical Parameters at Initiation of and During Combination Therapy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>T0b</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n) (once/twice HD)</td>
<td>0/0</td>
<td>52/0</td>
<td>25/9</td>
<td>19/8</td>
<td>17/10</td>
<td>9/7</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>59.7±10.0</td>
<td>58.8±10.2c</td>
<td>57.1±11.3c</td>
<td>58.2±10.6c</td>
<td>59.0±10.5</td>
<td>58.4±10.4c</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>151.5±25.3</td>
<td>140.6±25.2c</td>
<td>140.9±15.8c</td>
<td>144.4±35.5c</td>
<td>144.1±20.3c</td>
<td>139.4±17.7c</td>
</tr>
<tr>
<td>Urine volume (mL/24 hours)</td>
<td>438±225</td>
<td>228±206c</td>
<td>352±478</td>
<td>138±122c</td>
<td>93±117c</td>
<td>60±82c</td>
</tr>
<tr>
<td>UF on PD (mL/24 hours)</td>
<td>794±447</td>
<td>886±409</td>
<td>948±389c</td>
<td>967±533</td>
<td>908±471c</td>
<td></td>
</tr>
<tr>
<td>Urine UF (mL/24 hours)</td>
<td>914±463</td>
<td>928±446</td>
<td>904±564</td>
<td>949±437</td>
<td>800±403</td>
<td>905±451c</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>63.0±18.2</td>
<td>58.1±15.4c</td>
<td>55.9±18.1c</td>
<td>64.1±12.5</td>
<td>63.3±14.8</td>
<td>57.6±16.8c</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>13.1±3.3</td>
<td>12.5±2.6</td>
<td>12.5±2.8c</td>
<td>12.4±3.6c</td>
<td>12.8±3.3</td>
<td>12.2±3.2c</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL)</td>
<td>5.7±1.6</td>
<td>6.1±1.6</td>
<td>6.0±1.5</td>
<td>6.0±1.6</td>
<td>6.2±1.8c</td>
<td>5.7±2.2c</td>
</tr>
<tr>
<td>Serum β2-microglobulin (mg/L)</td>
<td>35.8±14.3</td>
<td>37.4±10.4</td>
<td>37.5±17.7</td>
<td>31.5±8.9c</td>
<td>33.2±11.4</td>
<td>33.2±7.9c</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.3±0.6</td>
<td>3.5±0.5c</td>
<td>3.5±0.4</td>
<td>3.5±0.3</td>
<td>3.5±0.5</td>
<td>3.6±0.5c</td>
</tr>
</tbody>
</table>

HD = hemodialysis; UF = ultrafiltration; PD = peritoneal dialysis; BUN = blood urea nitrogen.

a Excludes patients with urine volume ≤100 mL/24 hours.
b Before start of combination therapy.
c p < 0.05 versus T0.

Data are presented as mean±SD.

### TABLE 3

Changes in Clinical Signs and Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients [n (%)]</th>
<th>T0a</th>
<th>At 3 monthsb</th>
<th>p (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>12 (23.1%)</td>
<td>0</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>9 (17.3%)</td>
<td>4 (7.7%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuritis</td>
<td>7 (13.5%)</td>
<td>1 (1.9%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Restless legs</td>
<td>13 (25.0%)</td>
<td>3 (5.7%)</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>EPO-resistant anemia</td>
<td>15 (28.8%)</td>
<td>2 (3.8%)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>27 (51.9%)</td>
<td>3 (5.8%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

EPO = erythropoietin.

a Before start of combination therapy.
b Once-weekly hemodialysis in all patients.
Combination therapy also was initiated in this study due to a need to restrict the infused volume of dialysate for medical reasons, for example, hernia or hydrothorax. Combination therapy was performed in 1 patient with inguinal hernia and in 2 patients with hydrothorax and facilitated the continuation of PD therapy. Other indications for combination therapy include the concept of a “PD holiday,” which may improve the quality of life for patients undergoing long-term self-managed PD (19). Overall, the average duration of combination therapy was 24.5 months, suggesting that such a combination facilitates an extension of the duration of PD. In this study, the maximum duration of PD was 191 months, with 50 of those months being combination therapy.

Finally, the issue of health-care expenditure associated with implementation of combination therapy needs to be addressed. Although health insurance systems differ between countries, it is worth noticing that, in Japan, the cost is equivalent to or less than that of continuous ambulatory PD (CAPD), as well as of conventional HD, the least expensive blood purification method, and also far less expensive than automated PD. The dialysis costs in the Japanese system, including laboratory tests and management fees, have been estimated to be US$3346, US$2833, US$4649, and US$2769 per month for CAPD, HD, automated PD, and combination therapy (5 days PD and weekly HD), respectively (8). In the event combination therapy would be more expensive than conventional HD, the clinical benefits, side effects, and quality-of-life aspects of the two different options should be taken into account in the decision to switch a PD patient to combined therapy or HD only.

In conclusion, this study has shown that combination therapy with HD performed once to twice weekly is feasible and, in the studied patients, improved the clinical status of patients for whom adequate solute and/or fluid removal could not be achieved with standard PD alone. Combination therapy also has the potential of facilitating a substantial extension of the time patients are able to remain on PD. Combining PD and HD, therefore, constitutes an alternative to switching patients to HD-only treatment, allowing patients to benefit from the advantages of remaining on a continuous therapy for at least 5 – 6 days per week. These advantages relate to sodium and water removal, quality of life, and potentially RRF preservation, as indicated in the study by McIntyre (9). Moreover, it also provides an opportunity for reducing total glucose exposure, thereby increasing the likelihood of long-term membrane survival. This aspect may, for the future, influence the timing of when to start combination therapy in patients on PD. Further studies are also required to refine indications for a combined therapy and to identify criteria to determine when a full conversion to HD should occur. Finally, to highlight the conceptual benefits of combining HD and PD, it is proposed to rename combination therapy “complementary dialysis.”

In summary, the present study explored the potential benefits of combining HD and PD at a stage when PD-only therapy did not result in acceptable outcome. Thus, taken together, our and the study by McIntyre illustrate two different options of combining the two modalities, either early during the course of dialysis or when PD-only therapy is not sufficient. It appears that, based on these preliminary data, both options are feasible but that they provide different types of benefit. It is suggested that future research in this area should not only focus on confirming the results of these two reports, but should also evaluate the potential benefit of combination therapy in a third category, that is, in patients that do not have satisfactory outcome on HD-only therapy, as well as the impact of using novel PD solutions in “complementary dialysis.” Future potential indications for this new combined modality are summarized in Table 4.

**TABLE 4** Potential Indications for Combination Therapy with Peritoneal Dialysis (PD) and Hemodialysis (HD)

<table>
<thead>
<tr>
<th>1.</th>
<th>Patients in whom increased PD dose is not compatible with patient’s lifestyle or subjective tolerance of increased fill volume, with</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) insufficient small solute clearance resulting in</td>
<td></td>
</tr>
<tr>
<td>• uremic symptoms</td>
<td></td>
</tr>
<tr>
<td>• excessive potassium/sodium/phosphate and/or protein intake</td>
<td></td>
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<tr>
<td>(b) fluid overload due to</td>
<td></td>
</tr>
<tr>
<td>• ultrafiltration failure</td>
<td></td>
</tr>
<tr>
<td>• difficulty in managing fluid balance because of poor self-management</td>
<td></td>
</tr>
<tr>
<td>• severe heart failure</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Medical reasons for not increasing dialysate volume, e.g., limited peritoneal capacity, hernia, hydrothorax</td>
</tr>
<tr>
<td>3.</td>
<td>Severe mental stress due to PD; PD holiday *</td>
</tr>
<tr>
<td>4.</td>
<td>Peritoneal rest (with the expectation of improved peritoneal function/postponement of membrane deterioration)</td>
</tr>
<tr>
<td>5.</td>
<td>Prevention of complications related to the intermittent nature of HD, e.g., loss of residual renal function</td>
</tr>
<tr>
<td>6.</td>
<td>HD patients with cardiovascular instability</td>
</tr>
</tbody>
</table>

* See text.
REFERENCES


