Combined Therapy with Peritoneal Dialysis and Hemodialysis: A Multicenter Retrospective Observational Cohort Study in Japan

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Key Words
β2 microglobulin · Dialysate-to-plasma ratio of creatinine (D/P Cr) · Dialysis adequacy · Hemodialysis · Peritoneal dialysis · Peritoneal equilibration test (PET) · Residual renal function

Abstract
Background/Aims: Combining peritoneal dialysis (PD) and hemodialysis (HD) has been a common treatment option in Japan. Methods: In this retrospective, multicenter, observational study, the clinical characteristics and outcomes of 104 patients (57 ± 11 years, males 72%) who had switched from PD alone to combined therapy with PD and HD were studied. Clinical parameters were measured at baseline and after 3 months of combined therapy. Results: At baseline, urine volume, dialysate-to-plasma ratio of creatinine (D/P Cr), and total Kt/V were 150 ml/day (range: 0–2,000 ml/day), 0.67 ± 0.11, and 1.8 ± 0.4, respectively. During the first 3 months of combined therapy, body weight, urine volume, serum creatinine level, and D/P Cr decreased, whereas hemoglobin levels increased. Conclusions: In patients where PD does not result in acceptable outcomes, combined therapy with PD and HD may have potential benefits in terms of dialysis adequacy and hydration status.


Introduction

Although peritoneal dialysis (PD) is recommended as a first-line treatment for end-stage renal disease (ESRD) [1], the efficiency of PD gradually worsens over time. In Japanese PD patients, 5-year technique survival was esti-
imated to be 70%, and the most common reasons for this technique to become a failure are inadequate dialysis and/or ultrafiltration failure [2]. Treatment options for these patients include increasing the dose of PD, switching to hemodialysis (HD) or starting a combined therapy with PD and HD.

Combined therapy was first introduced in Japan in the 1990s, and from then on, it has rapidly gained popularity. It is a treatment choice for PD patients who cannot achieve adequate fluid and/or solute removal by PD alone. Generally, it comprises five to six days of PD combined with one HD session per week. In 2012, approximately 1,900 patients (20% of all PD patients) were on this therapy in Japan (Japanese Society for Dialysis Therapy, unpublished data).

Although there have been several published reports, most studies till date were limited by the population size or by being single-center studies [3–9]. To better evaluate the clinical benefit of this modality, we established the Evaluation of the Adequacy of Renal replacement THERapy (EARTH) Study Group. This paper presents the clinical outcomes of more than 100 patients on combined therapy across nine centers in Japan.

### Materials and Methods

#### Subjects

Inclusion criteria of this retrospective, multicenter, observational cohort study was switching from PD alone to combined therapy with PD and HD. We identified 104 patients (75 males and 29 females; mean age at the start of combined therapy: 57 ± 11) from nine facilities in Japan, including: Jikei University Hospital and three branch hospitals, Kawaguchi Municipal Medical Center; Toho University Omori Medical Center; Tokyo Medical University Hospital; Tokyo Women’s Medical University Medical Center East, and Saiseikai Central Hospital. All 104 patients switched from PD alone to combined therapy between November 1998 and November 2009. The study was conducted in accordance with the Declaration of Helsinki. Table 1 shows baseline patient characteristics. The median duration of PD at the start of the combined therapy was 37 months (range: 2–250 months) (fig. 1).

#### Combined Therapy Regimens

In general, PD was not carried out on the day of an HD session, and 57 patients (61%) also did not perform PD on another day, which was defined as a ‘PD holiday’. Twenty-six patients (26%) used automated PD, and 41 patients (41%) used icodextrin solution. Regarding the HD prescription, 81 patients (81%) received HD once a week for 4 h. Only two patients (2%) received HD twice a week. High-flux membranes were used for all HD sessions. Blood samples were drawn from the arterial line at the start of the HD treatment.

#### Study Outcomes

We compared the clinical and laboratory data on dialysis adequacy and volume status just before switching therapy with the data collected 3 months later. Study outcomes included changes in body weight, blood pressure, urine volume, peritoneal ultrafiltration volume, blood urea nitrogen (BUN), creatinine (Cr), β2 microglobulin, and hemoglobin. Additionally, changes in dialysate-to-plasma ratio of creatinine (D/P Cr), obtained from a peritoneal equilibration test (PET) were examined. The total Kt/V and total

<table>
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<tr>
<th>Table 1. Baseline patient characteristics (n = 104)</th>
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<td>Category</td>
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<td>Sex, %</td>
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<td>Age at the start of combined therapy, years</td>
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<td>Cause of ESRD</td>
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<td>Duration of PD at the start of combined therapy, months</td>
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PD = Peritoneal dialysis; CGN = chronic glomerulonephritis; PKD = polycystic kidney disease.
**Results**

At the start of combined therapy, urine volume, D/P Cr, total Kt/V, and total weekly Ccr were 150 ml/day (range: 0–2,000 ml/day), 0.67 ± 0.11, 1.8 ± 0.4, and 49.9 ± 13.1 ml/min/1.73 m², respectively (table 2). The results of the comparative analysis between the start of the combined therapy and 3 months later are also shown in table 2. Body weight decreased from 64.5 ± 14.8 kg to 63.4 ± 14.2 kg (p < 0.01). Neither systolic nor diastolic blood pressure changed significantly. Urinary volume decreased, whereas the peritoneal ultrafiltration volume did not change significantly. The mean serum creatinine levels decreased significantly from 12.9 ± 3.4 mg/dl to 12.3 ± 3.0 mg/dl (p < 0.01). Although BUN and β2 microglobulin levels tended to decrease, these decreases were not significant. Hemoglobin levels increased from 8.7 ± 1.5 g/dl to 10.3 ± 1.3 g/dl (p < 0.01). D/P Cr decreased significantly from 0.67 ± 0.11 to 0.61 ± 0.13 (p < 0.01) (fig. 2).

**Discussion**

In this multicenter retrospective observational cohort study, the clinical outcomes of combined therapy with PD and HD in Japan were evaluated. At the start of the combined therapy, the median PD duration was approx-
imately 3 years, which is similar according to the previous reports [3–6]. In the current study, body weight decreased following the initiation of combined therapy, suggesting that overhydration was a main cause for starting this therapy, whereas there was only a small change in solute clearance, including Kt/V and weekly Ccr, and circulating β2 microglobulin was not increased at baseline. During 3 months of combined therapy, both hydration status (represented by body weight and hemoglobin) and dialysis adequacy (represented by serum creatinine levels) were significantly improved as indicated in many previous reports [3, 5, 6, 9]. On the other hand, the change in serum β2 microglobulin levels did not reach significance. Unlike in PD, serum β2 microglobulin in patients receiving HD changes dramatically over a week, and we usually measure its highest value at the start of an HD session. Because the serum β2 microglobulin level was associated with mortality among HD patients [11], and was an independent risk factor for encapsulating peritoneal sclerosis (EPS) [12], the β2 microglobulin level is an important marker in the management of dialysis.

D/P Cr obtained by PET was dramatically decreased during this period, and this finding was also confirmed in our previous report [3]. There are several possible explanations for this. First, combined therapy could limit further deterioration of the peritoneal membrane by decreasing exposure to glucose and elimination of uremic toxins. Not only cumulative glucose exposure [13], but also uremia per se [14] are associated with structural alternations in the peritoneum. Second, peritoneal rest could have a positive impact on peritoneal function. Third, histological improvement of peritoneal edema secondary to improvement of fluid status might lead to the reduction in D/P Cr.

Combined therapy with PD and HD may also give rise to some concerns. Considering that the preservation of RRF is one of the most important factors for selecting standard PD, first it is a troubling observation that the urine volume decreased, whereas the peritoneal ultrafiltration volume did not change in the current study. Since there have been many reports showing the association between RRF and mortality among PD patients [15, 16], a decline in RRF by combined therapy might lead to a poor outcome. Second, although combined therapy would increase the overall duration of PD treatment, this could have some drawbacks. For example, it is well known that prolonged PD duration is an independent risk factor for EPS, Yamamoto et al. [17] reported that the cut-off point of PD duration for the development of EPS was approximately 10 years.

There are several limitations to the present study. First, we did not have a control group, and the observational design allows only limited conclusions. Second, data of erythropoietin-stimulating agents (ESA) and antihypertensive drug were not collected, making the interpretation of hemoglobin and blood pressure data difficult. Third, we did not evaluate the nutritional status. Because both body weight and creatinine levels decreased during 3 months of combined therapy, we cannot deny the possibility of impaired nutritional status with decrease in muscle mass. Fourth, there was no universal consensus on the indication for introduction or cessation of the combined therapy. To address these and other unanswered questions, a multicenter, prospective, observational study of patients switching from PD to combined therapy is planned.

Conclusions

In this large retrospective observational cohort study, both overhydration and inadequate dialysis appear to have been improved by switching from PD alone to combined therapy with PD and HD. Further studies are needed to clarify the indications for and consequences of switching from standard PD alone to combined therapy.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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