Changes in Peritoneal Transport and Peritoneal Damage in Japanese Patients Undergoing Peritoneal Dialysis Using Neutral-pH Dialysate: A Retrospective Cohort Study at Two Centers

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The effects of medium- or long-term use of neutral-pH dialysate on peritoneal transport and peritoneal damage have not been sufficiently researched.

We retrospectively evaluated time-dependent changes in the dialysate-to-plasma ratio of creatinine (D/P Cr) and biomarkers of peritoneal damage in the effluent of 65 patients who underwent peritoneal dialysis (PD) with neutral-pH dialysate, including 48 who underwent medium-term PD (≥3 years) and 17 who underwent long-term PD (≥5 years).

*Patients who underwent medium-term PD initially had a D/P Cr of 0.59 (range: 0.53 – 0.74), nonsignificantly changing to 0.65 (range: 0.55 – 0.73), 0.67 (range: 0.56 – 0.74), and 0.67 (range: 0.62 – 0.72) after 1, 2, and 3 years respectively (*p = *0.30,* p = *0.26, and* p = *0.19). Patients who underwent long-term PD initially had a D/P Cr of 0.57 (range: 0.52 – 0.62), nonsignificantly changing to 0.61 (range: 0.52 – 0.69), 0.64 (range: 0.54 – 0.67), 0.62 (range: 0.57 – 0.66), 0.65 (range: 0.50 – 0.72), and 0.61 (range: 0.48 – 0.7) after 1, 2, 3, 4, and 5 years respectively (*p = *0.49,* p = *0.31,* p = *0.24,* p = *0.23, and* p = *0.46). After 3 years, a significant increase in effluent hyaluronan (HA) from 90 ng/mL initially (range: 66 – 121 ng/mL) to 144 ng/mL (range: 116 – 216 ng/mL) was observed (*p = *0.04).*

No significant change in D/P Cr was observed in patients who underwent PD with neutral-pH dialysate. However, effluent HA, which is a biomarker for peritoneal damage, increased. In patients using neutral-pH dialysate, D/P Cr cannot be a biomarker for determining PD discontinuation within 5 years, but effluent HA might be useful.

Key words
Neutral dialysate, peritoneal damage, peritoneal equilibration test

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Introduction

Peritoneal dialysis (PD) is one of the main treatments in renal replacement therapy. However, in Japan, the PD guidelines recommend that PD be discontinued in view of the risk of encapsulating peritoneal sclerosis (EPS) and that peritoneal equilibration tests (PETs) be regularly performed to determine membrane status when damage is suspected in patients undergoing long-term PD or in those who have experienced peritonitis (1). However, the guidelines were created based on research results dating back more than 10 years, and we believe that they are based on a large number of cases in which acidic dialysate was used.

During the period in which mainly acidic dialysate was used, peritoneal permeability was known to gradually increase in patients undergoing long-term PD (2). In Japan, neutral-pH dialysate became available in 2000. Today, it is the standard dialysate. However, the effects of the medium- or long-term use of neutral-PH

dialysate on peritoneal transport and peritoneal damage have not been sufficiently researched. In the present study, we therefore retrospectively evaluated time-dependent changes in the dialysate-to-plasma ratio of creatinine (D/P Cr), which is an indicator of peritoneal transport capacity for small molecules, and biomarkers of peritoneal damage in effluent [hyaluronan (HA), cancer antigen 125 (CA125), and D-dimer] from PD start in patients who underwent medium- or long-term PD with neutral-pH dialysate.

Methods

Between March 2005 and August 2016, 192 patients 18 years of age or older started PD using neutral-pH dialysate alone (patients using icodextrin included) at our hospital and at St. Marianna University School of Medicine Hospital. We conducted a retrospective observational study of 48 patients who underwent medium-term PD (≥3 years) and 17 patients who underwent long-term PD (≥5 years). The study was approved by the medical ethics committee of Kawasaki Municipal Tama Hospital.

Data extracted from the medical records for the study patients included age, sex, underlying disease, duration of PD, history of peritonitis, use of a 2.5% glucose solution, use of icodextrin, initial dialysis dose, estimated glomerular filtration rate at the start of PD, 4-hour D/P Cr as tested by PET every 6 months from PD start, and biomarkers (HA, CA125, D-dimer) in 4-hour effluent.

The standard PET invented by Twardowski (3) was performed every 6 months after PD start. The D/P Cr was calculated based on the 4-hour effluent and 2-hour plasma values. The first PET performed within 2 – 3 months of PD start was regarded as the baseline. Peritoneal transport was classified into 4 categories (low, low-average, high-average, high). When a peritonitis episode occurred, the PET was performed at least 3 months after the peritonitis episode had subsided. The PET was also performed earlier if the patient experienced ultrafiltration failure. Exclusion criteria were hemodialysis before PD start and combined therapy with PD and hemodialysis.

Data are expressed as medians with interquartile range. For comparisons of paired data, a nonparametric Wilcoxon signed-rank test was used. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics software application (version 24: IBM Japan, Tokyo, Japan).

Results

Figure 1 shows time-dependent changes in the PET classification for the study patients. Although the low and low-average categories tended to decrease up to 3 years after PD start, the ratio of the categories did not change after 4 or 5 years.

The patients on medium-term PD included 31 men and 17 women. The primary disease was diabetes in 23 patients; 25 patients were nondiabetic. Median age in the group was 63.3 years (range: 57 – 69 years). The median duration of PD was 49 months (range: 43 – 64 months). Fourteen patients had a history of peritonitis. Eleven patients used 2.5% glucose solution, and ten used icodextrin. The median initial daily dialysate volume was 5.75 L (range: 4 – 6 L), and the median estimated glomerular filtration rate at PD start was 6.0 mL/min/1.73 m^2 (range: 5.0 – 6.9 mL/min/1.73 m^2; Table I). The median initial D/P Cr was 0.59 (range: 0.53 – 0.74); it was 0.65 (range: 0.55 – 0.73) after 1 year, 0.67 (range: 0.56 – 0.74) after 2 years, and 0.67 (range: 0.62 – 0.72) after 3 years. Those changes were nonsignificant: $p = 0.30$, $p = 0.26$, and $p = 0.19$ respectively (Figure 2).

Of the 9 men and 8 women on long-term PD (≥5 years), 5 patients had diabetes as their primary disease; the remaining 12 were nondiabetic. Median age in the group was 62.0 years (range: 51 – 69 years). The median duration of PD was 68 months (range: 65 – 75 months). Six patients had a history of peritonitis. Two patients used 2.5% glucose solution, and three used icodextrin. The median initial daily dialysate volume was 5.5 L (range: 4.5 – 6 L), and the median estimated glomerular filtration rate at PD start was 5.9 mL/min/1.73 m^2 (range: 4.7 – 6.4 mL/min/1.73 m^2; Table I). Figure 1

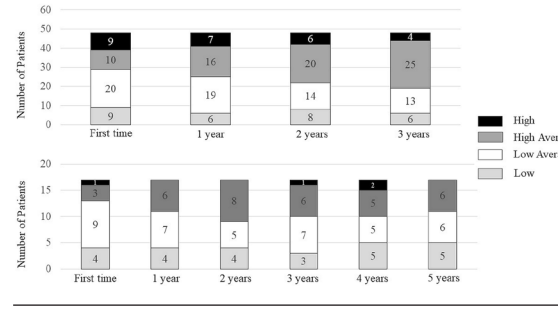

FIGURE 1 Time-dependent changes in the peritoneal equilibration test classification in peritoneal dialysis patients treated for 3 years (top panel) and 5 years (bottom panel).

shows changes in the PET classification. The initial median D/P Cr was 0.57 (range: 0.52 – 0.62); it changed to 0.61 (range: 0.52 – 0.69) after 1 year, 0.64 (range: 0.54 – 0.67) after 2 years, 0.62 (range: 0.57 – 0.66) after 3 years, 0.65 (range: 0.50 – 0.72) after 4 years, and 0.61 (range: 0.48 – 0.7) after 5 years. Those changes were nonsignificant: $p = 0.49$, $p = 0.31$, $p = 0.24$, $p = 0.23$, and $p = 0.46$ respectively (Figure 3).

In 13 patients, median effluent HA was 90 ng/mL (range: 66 – 121 ng/mL) initially, rising to 113 ng/mL (range: 77 – 248 ng/mL) after 1 year and 110 ng/mL (range: 81 – 156 ng/mL) after 2 years, a nonsignificant change ($p = 0.47$ and $p = 0.30$ respectively). However, effluent HA increased significantly to 144 ng/mL (range: 116 – 216 ng/mL) after 3 years ($p = 0.04$, Figure 4). No time-dependent changes in effluent CA125 and D-dimer were observed.

TABLE 1 Characteristics of patients undergoing medium-term (3 years or more) and long-term (5 years or more) peritoneal dialysis (PD)

Variable	*Patients treated for* ≥3 *Years*	≥5 *Years*
Age (years)		
Median	63	62
IQR	57–69	51–69
Sex [*n* (%) men]	31 (65)	9 (53)
Prevalence of DM [*n* (%)]	23 (48)	5 (29)
Duration of PD (months)		
Median	49	68
IQR	43–64	65–75
Peritonitis episodes [*n* (%)]	14 (29)	6 (35)
Use of dialysate with [*n* (%)]		
2.5% Dextrose	11 (23)	2 (12)
Icodextrin	10 (21)	3 (18)
Initial daily dialysate dose (L)		
Median	5.75	5.5
IQR	4–6	4.5–6
eGFR at PD start (mL/min/1.73 m^2)		
Median	6.0	5.9
IQR	5.0–6.9	4.7–6.4
D/P Cr at initial PET		
Median	0.59	0.57
IQR	0.53–0.74	0.52–0.62

IQR = interquartile range; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; D/P Cr = dialysate-to-plasma ratio of creatinine; PET = peritoneal equilibration test.

Discussion

Prior studies of medium- and long-term time-dependent changes in D/P Cr are limited in number, and studies focusing PD with neutral-pH dialysate are even more limited. Chen *et al.* (4) evaluated changes in D/P Cr during a 4-year period and reported that, as in the present study, no time-dependent changes in D/P Cr were observed in subjects 60 years of age and older and that D/P Cr declined in subjects less than 60 years of age. Moreover, Lee *et al.* (5) evaluated changes in D/P Cr during a 7-year period and reported that no changes were observed. Jiang *et al.* (6) evaluated changes in D/P Cr during an even longer 10-year period. They reported that, although a decrease in D/P Cr was observed after 2 years compared with the initial D/P Cr, the D/P Cr remained similar for the subsequent few years, with a tendency to increase slightly up to the 5th year. Compared with the 2nd year (during which the D/P Cr was lowest), a

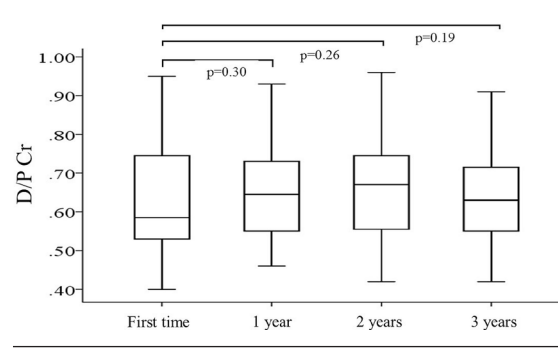

FIGURE 2 Changes in the dialysate-to-plasma ratio of creatinine (D/P Cr) in peritoneal dialysis patients treated for 3 or more years.

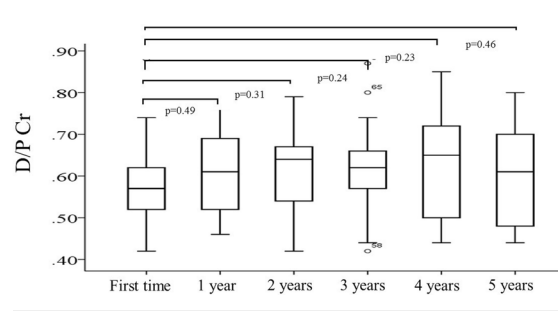

FIGURE 3 Changes in the dialysate-to-plasma ratio of creatinine (D/P Cr) in peritoneal dialysis patients treated for 5 or more years.

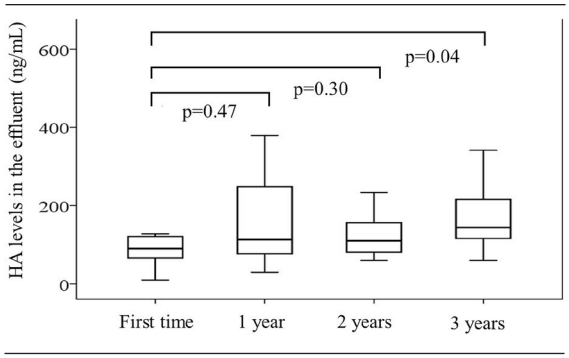

FIGURE 4 Changes in effluent hyaluronan (HA) in peritoneal dialysis patients treated for 3 or more years.

significant difference in the D/P Cr was observed in the 7th and 10th years, even though, compared with the initial D/P Cr, no significant differences were observed during the 10-year period. However, the foregoing studies did not focus on neutral-pH dialysate alone.

In the *bal*ANZ trial, Johnson *et al.* (7) reported that the D/P Cr was maintained at stable levels after 2 years in patients who were using a neutral-pH PD solution low in glucose degradation products. Although a few other studies have evaluated time-dependent changes in D/P Cr in patients on neutral-pH dialysate, the observation period has been 1 – 2 years (8,9), which is shorter than the observation periods considered in the present study. In the present study, all patients were using only neutral-pH dialysate. The results of the present study show that the D/P Cr showed no increase until the 3rd year or by the 5th year.

The Japanese PD guidelines advise that PD discontinuation should be considered for patients showing a time-dependent increase in D/P Cr and in whom peritoneal permeability remains high for 12 months or longer (as classified by PET), because those characteristics are considered to indicate highly advanced peritoneal damage. In the present study, a time-dependent increase in D/P Cr or continuously high peritoneal permeability was observed in only 2 patients (4.2%) during the 3-year observation period. The authors of the NEXT-PD study of patients on neutral-pH dialysate reported that 13.2% of patients who had been receiving continuous PD for approximately 3 years were classified as having high peritoneal permeability (10). The percentage in the present study was even lower.

It is possible that patients with continuously high peritoneal permeability and those with a time-dependent increase in D/P Cr are fewer in number now that neutral-pH dialysate is mostly used. Multiple episodes of peritonitis (11), the use of hypertonic solutions (12), advanced age (5), and male sex (5,13) have been reported to be factors affecting D/P Cr. Although we examined D/P Cr by dividing our study patients into two groups based on the presence or absence of those risk factors, we observed no significant difference in time-dependent changes of D/P Cr (data not shown). The reasons for that lack of results might be that the number of patients with multiple episodes of peritonitis was small (6 patients in the 3-year observation period: 5 with 2 episodes and 1 with 3 episodes; and 3 patients in the 5-year observation period: 2 with 2 episodes and 1 with 3 episodes) and that patients using 2.5% glucose solution might have had little exposure to glucose. Davies *et al.* (14) reported that exposure to glucose had an effect on D/P Cr. However, most of our patients using 2.5% glucose solution used only 1 bag daily, and most patients started dialysis with incremental PD, in which the initial dialysis dose is small. Exposure to glucose might therefore have been less in our patients than in patients in other studies.

In the present study, effluent HA increased significantly even though no time-dependent changes in D/P Cr were observed. Effluent HA (15) and coagulation factors including D-dimer (16), interleukin 6 (17), and CA125 (18) have been reported to be biomarkers indicating peritoneal damage. In particular, effluent HA has been reported to increase in response to chronic intraperitoneal inflammation (19). Although we observed no time-dependent change in D/P Cr in our patients, the increased effluent HA suggested the presence of chronic intraperitoneal inflammation even when patients were using neutral-pH dialysate. However, more evidence is required to determine whether increased effluent HA is a risk factor for EPS.

The present study has a few limitations. First, the sample size was small compared with those in previous studies. A second limitation was the retrospective observational design, in which the analysis results do not include D/P Cr data from patients who dropped out of PD within 3 years. However, during the observation period, no patient undergoing PD at either of the 2 centers developed EPS, and no patients discontinued PD because of increased D/P Cr. A prospective study of time-dependent changes in D/P Cr and effluent biomarkers in patients on neutral-pH dialysate, with an even longer observation period, is required.

Conclusions

The present study showed no time-dependent changes in D/P Cr in patients using neutral-pH dialysate during the observation period of 3 – 5 years. We previously reported that increased D/P Cr is related to fluid overload in patients undergoing PD (20), and therefore D/P Cr might not reflect peritoneal permeability alone. However, patients might be able to remain on PD for a longer period of time in the future if the use of neutral-pH dialysate maintains peritoneal transport capacity and reduces peritoneal damage. An evaluation not only of D/P Cr, but also of multiple other items including effluent biomarkers, is therefore desirable for guiding that decision. We observed no significant changes in D/P Cr in patients undergoing medium- to long-term PD with neutral-pH dialysate. Identification of a biomarker that acts as an indicator for PD discontinuation and a predictor of EPS is awaited.

Disclosures

We understand that *Advances in Peritoneal Dialysis* requires disclosure of any conflicts of interest, and we declare that we have no conflicts to disclose.

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