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Original Article

ORIGINAL ARTICLE

Short-term peritoneal rest reduces peritoneal solute transport rate and increases ultrafiltration in high/high average transport peritoneal dialysis patients: a crossover randomized controlled trial

Bei Wu, Huiping Zhao, Li Zuo, Aichun Liu, Lixia Lu, Jie Qiao, Xinxin Chu, Chuncui Men and Yuting He

Department of Nephrology, Peking University People's Hospital, Beijing, China

Correspondence to: Zhao Huiping; E-mail: huipingzhao2009@163.com

ABSTRACT

Background. The peritoneal solute transport rate (PSTR) tends to increase over time in some patients undergoing peritoneal dialysis (PD), potentially leading to ultrafiltration (UF) failure. Previous case reports have shown a significant decrease in PSTR and subsequent recovery of UF after discontinuing PD for a while. Therefore, we conducted a randomized controlled crossover study to evaluate the impact of short-term peritoneal rest on PSTR.
Methods. The study involved 14 continuous ambulatory peritoneal dialysis (CAPD) patients with high/high-average transport rate. Two groups were randomly assigned different treatment sequences: one group underwent daily intermittent peritoneal dialysis (IPD) for 4 weeks followed by CAPD, while the other group initially received CAPD treatment for 4 weeks and then switched to IPD. Peritoneal equilibration tests were performed before and after each treatment to evaluate PSTR and paired *t*-tests were used to compare the changes. Volume load, serum potassium and other clinical indicators were monitored at the same time.
Results. Short-term peritoneal rest (daily IPD) significantly reduced PSTR, with a decrease in the dialysate:plasma creatinine ratio from 0.71 ± 0.05 to 0.65 ± 0.07 ($P < .001$). Additionally, ultrafiltration significantly increased from 210 ± 165 ml to 407 ± 209 ml ($P = .001$). But there were no significant changes in interleukin-6 and vascular endothelial growth factor of PD effluent. No serious adverse events such as hypotension or hyperkalaemia occurred.
Conclusions. In PD patients with high and high-average transport, a 4-week period of short-term peritoneal rest by switching from CAPD to IPD (without long dwell) can lead to reductions in PSTR and increases in UF volumes, while maintaining clinical safety.

Keywords: intermittent peritoneal dialysis, peritoneal membrane, peritoneal rest, peritoneal solute transport rate, ultrafiltration

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KEY LEARNING POINTS

What was known:

- Case reports suggest that there is an increase in ultrafiltration (UF) volume and a decrease in peritoneal solute transport rate (PSTR) following a pause in peritoneal dialysis (PD; peritoneal rest) of days to months.

This study adds:

- This randomized controlled trial showed that the PSTR decreased and UF volume increased in PD patients with high and high-average transport after 4 weeks of short-term peritoneal rest (without long dwell).

Potential impact:

- The use of short-term peritoneal rest for improving PD UF could be a simple, effective and safe method.

INTRODUCTION

Peritoneal dialysis (PD) is a blood purification method that utilizes the peritoneum, a membrane within the body, as the dialysis membrane. The peritoneal solute transport rate (PSTR) plays a crucial role in determining the effectiveness of PD. PD patients with high/high-average transport often experience poor ultrafiltration (UF) when using glucose dialysate, due to faster glucose transport and a short maintenance of the osmotic pressure gradient. Previous studies have demonstrated that the PSTR increases over time during PD in some patients, which can eventually result in UF failure [1]. Consequently, this can lead to the discontinuation of PD. Therefore, nephrologists have been actively exploring methods to decelerate or potentially reverse the elevated rate of peritoneal solute transport.

Several case reports have documented instances of PD patients exhibiting a high PSTR and experiencing UF failure. However, it has been observed that after discontinuing PD for several days to months, there is a notable decrease in the PSTR and a subsequent recovery of UF [2, 3]. In other words, the PSTR appears to decrease following peritoneal rest. But previous cross-sectional studies have demonstrated that there is no discernible variation in the PSTR between ambulatory PD (partially absent daytime dwell) and continuous ambulatory PD (CAPD) [4]. Is the lack of separate analysis for nocturnal intermittent PD (IPD) and continuous cycle PD the reason for this? Or is it due to insufficient peritoneal rest time? Further research is required to address these questions.

Thus we designed a randomized controlled crossover trial in high/high-average transport PD patients. The objective of this study was to assess the disparity in the PSTR between intermittent and continuous dialysis in a single patient.

MATERIALS AND METHODS

Study design

This study was conducted at a single centre and followed a prospective randomized controlled crossover design. The aim of the study was to assess the impact of peritoneal rest (daily IPD) on PSTRs. Additionally, the study also aimed to monitor the safety and feasibility of this dialysis method. The study was performed in accordance with the principles of standard clinical practice and the guiding principles detailed in the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of Peking University People's Hospital (2022PHB386-001). All patients gave fully informed written consent to participate. The trial is registered at ClinicalTrials.gov (NCT05805813).

Patient selection

The study included participants who met the following criteria: CAPD for >3 months, PSTR with high/high-average transport [4-hour dialysate:plasma creatinine ratio (D:Pcr) >0.65 in a peritoneal equilibration test (PET)] and voluntary signed informed consent.

Exclusion criteria for this study include patients who have experienced peritonitis within the past 3 months; patients who have experienced acute complications such as cardiovascular events, pulmonary infections and gastrointestinal bleeding within the past 3 months; and patients who are deemed unsuitable for this study by physicians for other reasons.

Study procedures

During the baseline visit, all patients who consented and were recruited for the study were assigned a subject number in sequential order. The formation of random groups is based on pre-generated Excel (Microsoft, Redmond, WA, USA) random tables.

Recruited patients were asked to return for a baseline visit within 2 days. At the baseline visit, patients were randomly assigned to two groups (in a 1:1 ratio): the IPD-first group and the CAPD-first group (control group). In the IPD-first group, patients underwent dialysis for 10–14 hours/day (performing three or four exchanges in during the day, without a long overnight dwell, or utilizing an automated PD machine for nocturnal IPD, without a long daytime dwell). In contrast, patients in the CAPD-first group underwent dialysis continuously 24 hours/day. The treatment duration was 4 weeks, followed by a crossover of patients into another group for an additional 4-week treatment period (Fig. 1). The daily dialysate dose remained consistent between IPD and CAPD within the same patient and the dialysate concentration was adjusted based on clinical needs.

Sample collection and laboratory analysis

During each follow-up visit, the patient's clinical manifestations, fluid status (overhydration was measured using a body composition monitor) and PD prescription (PD modality, dosage and dialysate glucose concentration) were documented. A standard PET was administered. All serum and dialysate biochemical parameters were measured using an automatic biomedical analyser. Both 24-hour urine and PD effluent were collected at the same time to calculate urea clearance (weekly; Kt/V) and creatinine clearance. Simultaneously, a 4-hour PD effluent was collected and interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) were quantified using an enzyme-linked immunosorbent assay.

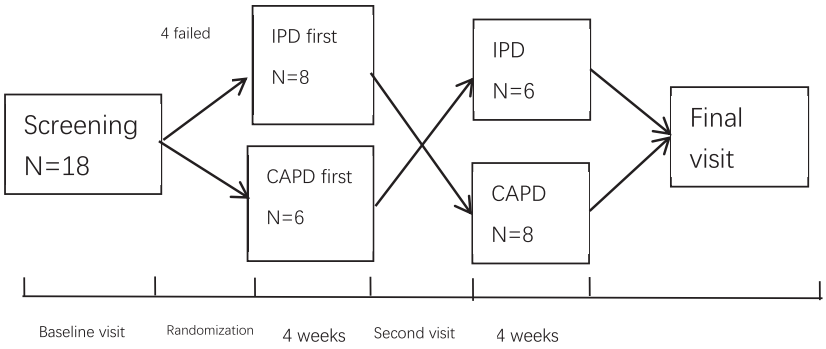


Figure 1: Schematic diagram illustrating the trial.

Study outcomes

The primary endpoint was the alteration in 4-hour D:Pcr and UF at the PET. Secondary endpoints included modifications in clinical manifestations, fluid status, biochemical parameters and changes in IL-6 and VEGF levels in the PD effluent.

Statistical analyses

Using a crossover design, a sample size of 11 was calculated using a level of significance of 0.05, a power of 0.90, an estimated standard deviation (SD; of 4-hour D:Pcr) of 0.04 and a minimal detectable difference in D:Pcr of 0.04. To account for potential dropouts, 14 patients were planned for enrolment. Only patients completing the trial were included in the analyses.

Descriptive statistics were presented as numbers for categorical data and mean ± SD for normal distribution continuous variables or median [interquartile range (IQR)] for non-normal distribution continuous variables. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. In case of normal distribution, comparison was performed using the paired two-tailed *t*-test, and a Welch test was used in case of unequal variances (assessed using the *F*-test). If the data did not follow a normal distribution, the Wilcoxon rank-sum test should be employed. A two-sided *P*-value $<.05$ was considered statistically significant. Statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA).

RESULTS

Between April and November 2023, a total of 18 patients were screened for this study. Of these, four patients were excluded from the screening process due to an unqualified 4-hour D:Pcr. The remaining 14 individuals were randomly enrolled and successfully completed the follow-up. Eight participants were assigned to the IPD-first group and six participants to the CAPD-first group. It is worth noting that no serious adverse events were observed during the study's follow-up period.

Baseline demographics and clinical characteristics

The mean age of the 14 participants was 56.9 ± 8.3 years, with 9 (64.3%) being male. In terms of primary diseases, there were 7 (50%) patients with chronic glomerulonephritis, 5 (35.7%) with diabetic nephropathy and 2 (14.3%) with chronic interstitial nephritis. The average 4-hour D:Pcr of the participants was 0.70 ± 0.40 (Table 1). In this study, the concentration of dialysate during IPD was prescribed to be lower than the concentration of dialysate during CAPD in 7 (50%) patients.

Table 1: Baseline demographic and clinical characteristics of the study participants (N = 14).

Characteristics	Values
Age (years), mean ± SD	56.9 ± 8.3
Male, *n* (%)	9 (64.3)
Cause of kidney failure, *n* (%)	
Glomerulonephritis	7 (50.0)
Diabetic nephropathy	5 (35.7)
Interstitial nephritis	2 (14.3)
Dialysis vintage (months), median (IQR)	42 (20.3–128.8)
Body mass index (kg/m^2), mean ± SD	22.9 ± 3.1
Blood pressure (mmHg), mean ± SD	
Systolic	126.9 ± 13.0
Diastolic	80.1 ± 10.3
24-hour urine output (ml), median (IQR)	150 (0–850)
4-hour D:Pcr, mean ± SD	0.70 ± 0.04

Primary endpoint analysis

Prior to undergoing short-term peritoneal rest (IPD), the 4-hour D:Pcr was measured at 0.71 ± 0.05, with a UF volume of 210 ± 165 ml during the PET. Following 4 weeks of IPD, the 4-hour D:Pcr decreased to 0.65 ± 0.07, while the UF volume increased to 407 ± 209 ml. These changes in D:Pcr ($P < .001$) and UF volume ($P = .001$) were found to be statistically significant. Conversely, before and after continuous PD, there were no significant changes observed in the 4-hour D:Pcr or the UF volume during the PET (Table 2 and Fig. 2).

Secondary clinical endpoint analyses

Under the condition that the total dialysis dose remained unchanged, the patient experienced an increase in multiple toxins after changing from CAPD to IPD. Urea levels increased from 19.6 ± 5.1 mmol/l to 22.8 ± 5.8 mmol/l, creatinine levels increased from 985 ± 254 μmol/l to 1157 ± 381 μmol/l, serum phosphorus rose from 1.38 ± 0.25 mmol/l to 1.71 ± 0.37 mmol/l, serum potassium rose from 4.22 ± 0.44 mmol/l to 4.61 ± 0.45 mmol/l and carbon dioxide decreased from 27.4 ± 2.4 mmol/l to 25.2 ± 3.1 mmol/l. However, the patient's overall

Table 2: Changes in the main parameters of PET before and after IPD and CAPD.

	IPD				CAPD			
Parameters	Before	After	t	P-value	Before	After	t	P-value
4-hour D:Pcr	0.71 ± 0.05	0.65 ± 0.07	4.932	<.001	0.66 ± 0.06	0.69 ± 0.07	−2.077	.058
4-hour UF (ml)	210 ± 165	407 ± 209	−4.178	.001	379 ± 240	264 ± 221	1.808	.094

volume load decreased and overhydration decreased from 2.8 ± 1.3 l to 2.3 ± 1.5 l. All of these changes were statistically significant.

Nearly half of the patients converting from IPD to CAPD had notable changes in their biochemical markers. Urea levels decreased from 21.7 ± 6.9 mmol/l to 19.2 ± 5.0 mmol/l, serum phosphorus levels decreased from 1.60 ± 0.38 mmol/l to 1.41 ± 0.32 mmol/l and serum potassium levels decreased from 4.59 ± 0.54 mmol/l to 4.20 ± 0.51 mmol/l. Additionally, there was an increase in overhydration from 2.6 ± 1.5 l to 3.2 ± 1.9 l. The differences observed were statistically significant (Table 3). The level of inflammation, as indicated by high-sensitivity C-reactive protein, did not show significant changes before or after IPD or CAPD.

During the entire trial, no serious adverse events such as hypotension and hyperkalaemia occurred.

Changes of parameters in dialysis effluent

PD effluent was analysed before and after both IPD and CAPD, showing no significant changes in IL-6, a marker of inflammation, and VEGF, a marker of neovascularization (Table 4).

DISCUSSION

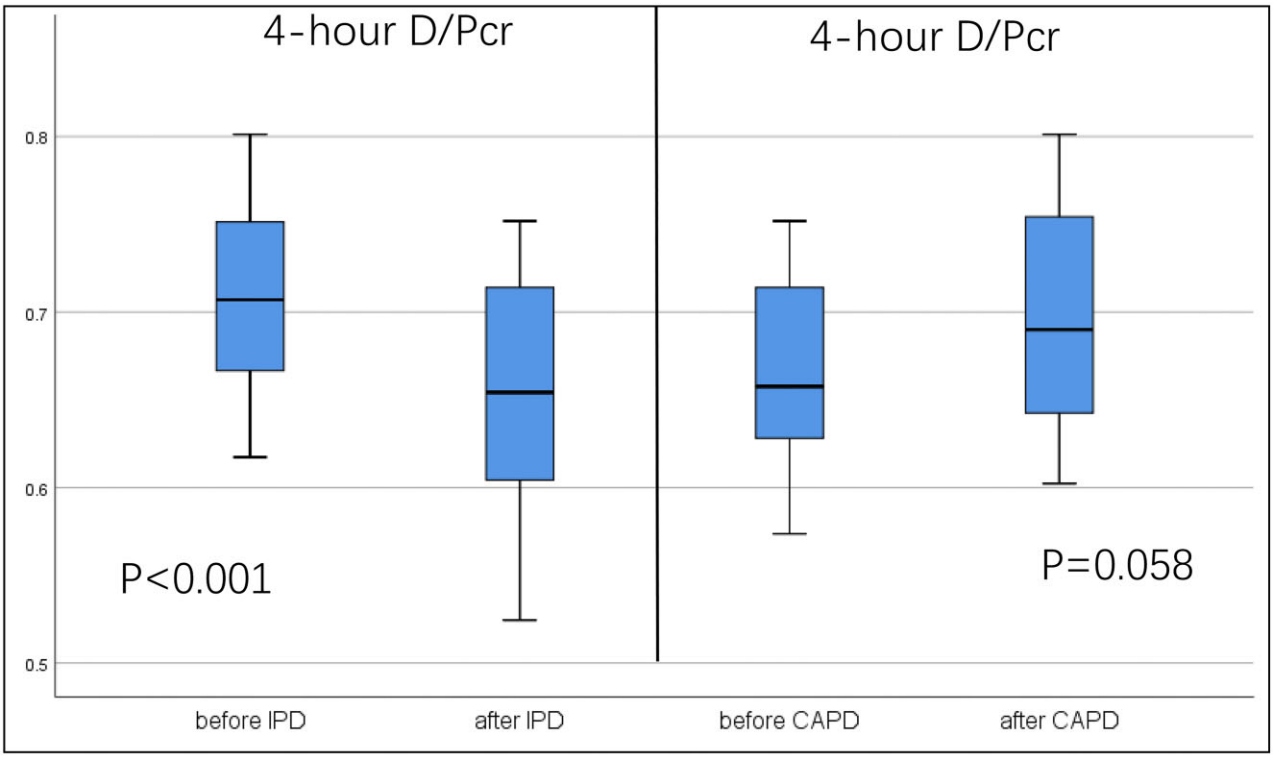
PD is a significant method of renal replacement therapy for patients with renal failure. In addition to solute clearance, volume management is equally crucial in PD patients. According to a multicentre study conducted in Europe, it was found that 25.2% of patients undergoing PD experience severe fluid overload [5]. The clearance of fluid depends on residual renal function and various conditions of the peritoneum. Since Twardowski's initial description of the PET in 1987 [6], it has remained the most widely employed method for assessing PSTR up to the present time. Among various factors, fast PSTR is a significant contributor to inadequate peritoneal fluid clearance. Numerous studies have indicated that patients with fast PSTR tend to have a poorer prognosis, with increased rates of hospitalization and even higher technique failure and mortality [7, 8].

PSTR is influenced by various factors. The Early CANUSA Study [9] and ANZDATA Registry [10] have identified older age, male gender, diabetes and cardiovascular disease as factors associated with high PSTR. Furthermore, numerous studies [11–13] conducted in the past decade have shown a strong correlation between high PSTR and local inflammation in the abdominal cavity, as indicated by increased levels of IL-6. Another study has shown that VEGF levels in both the serum and peritoneal dialysate of patients with high PSTR were significantly elevated [14]. This finding indirectly suggests that neovascularization and inflammation play a role in promoting an increase in the PSTR.

A study [1] was conducted on a group of patients who had undergone PD for a period of 5 years. The study found that PSTR remained stable for some patients, while it showed an increasing trend for others. A significant difference was observed in the glucose exposure in the PD fluid between these two groups. Patients with an increased PSTR had considerably higher glucose exposure compared with patients with a stable PSTR. Simultaneously, the group of patients with elevated PSTR exhibited poorer residual renal function, which could explain their requirement for a higher concentration of glucose in the PD solution. The combination of diminished residual renal function and increased glucose exposure contributes to an increase in PSTR and a decrease in UF, necessitating the use of a more concentrated glucose peritoneal dialysate to maintain the overall output. Consequently, this creates a detrimental cycle.

Previous animal experiments and case reports have demonstrated that suspending PD can reverse the increase in PSTR and enhance UF. In a study conducted by Kim *et al.* [15], rats were divided into three groups: group 1 served as the control group without PD, group 2 underwent PD for 4 weeks and group 3 received PD for 4 weeks followed by a 3-week cessation of dialysis. The findings revealed that after 4 weeks, both groups 2 and 3 exhibited significantly higher PSTR levels compared with group 1. However, after the 3-week period of dialysis discontinuation, the PSTR of group 3 decreased compared with its previous level. Zareie *et al.* [16] conducted similar animal experiments, where it was observed that the density of peritoneal blood vessels increased significantly after 5 weeks of PD in rats. However, it was found that this increase was reversible, as the density of blood vessels decreased after 12 weeks of stopping PD. Rodrigues *et al.* [2] reported a study on 12 patients who experienced long-term post-PD UF failure (PSTR 0.88 ± 0.09). Of these patients, 11 temporarily discontinued PD and switched to haemodialysis (HD) for a minimum of 30 days. The study found that in eight patients the UF failure was alleviated, allowing them to resume PD for a duration ranging from 5 to 29 months. Ueda *et al.* [3] reported four cases of patients who underwent PD combined with HD. The patients underwent PD for 5 days each week and HD on day 6. The study found that when the patients suspended PD for 2 days, the UF volume of PD on the first day after suspension was significantly higher than on day 5. These findings suggest that IPD may have the potential to reverse the increase in PSTR.

However, the current research consists of animal experiments and case reports, lacking a randomized controlled trial (RCT). Additionally, the duration of discontinuation of PD varies greatly, ranging from 2 days to several months, making it challenging to implement on a large scale in clinical practice. In clinical practice, daily IPD, which entails a brief peritoneal rest period of 10–14 hours/day, is not uncommon. This approach allows patients to rest their peritoneum without the need to resort to alternative blood purification methods. However, the effects of short-term discontinuation (10–14 hours) of PD on PSTR and UF volume have not been reported. To address these gaps, we designed and conducted an RCT to investigate the impact of short-term discontinuation of PD on PSTR and UF volume. The study findings indicated that in PD patients whose D:Pcr was >0.65, there was a significant decrease in PSTR and an increase in UF after 4 weeks of short-term discontinuation of PD (conversion



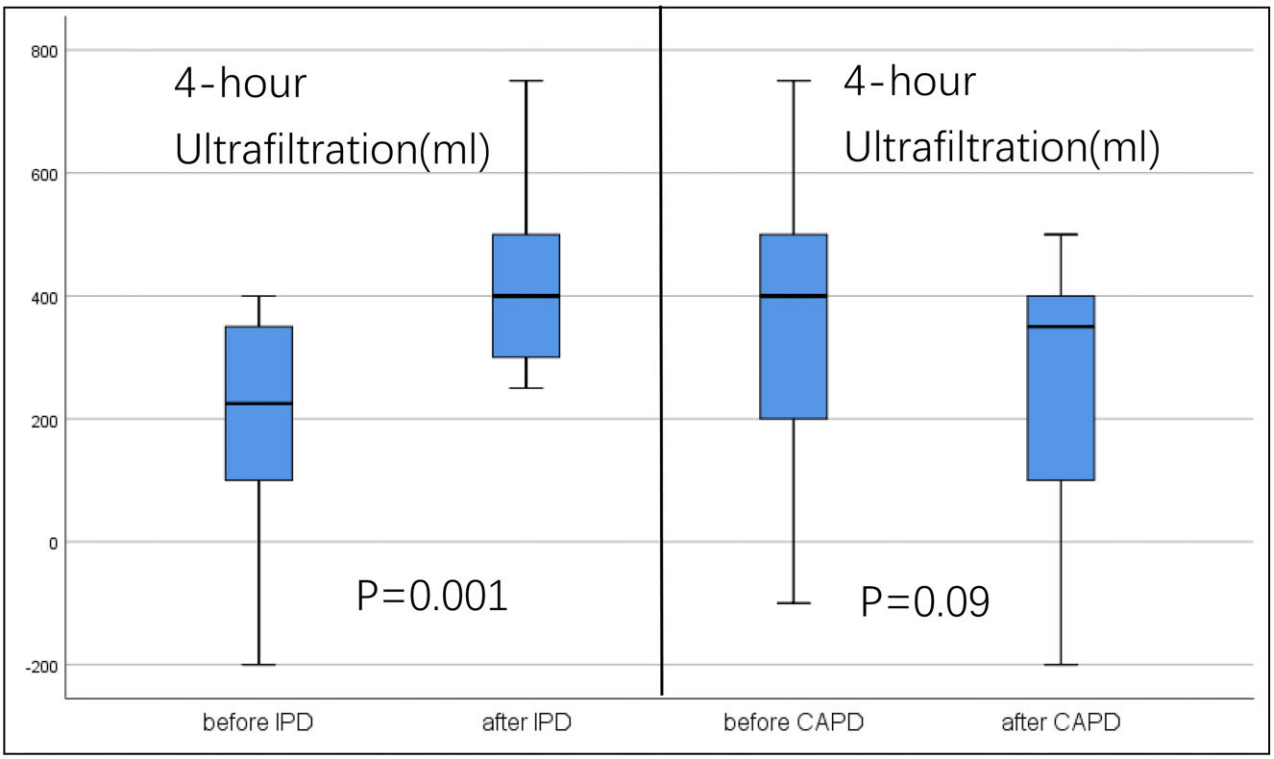


Figure 2: Changes of in main parameters of PET before and after IPD and CAPD.

Table 3: Changes in the main parameters before and after IPD and CAPD.

	IPD				CAPD			
Parameters	Before	After	t/Z	P-value	Before	After	t/Z	P-value
Weight (kg)	64.8 ± 11.0	63.9 ± 11.0	2.036	.063	64.1 ± 10.8	64.3 ± 10.1	−1.009	.331
Urine output/day (ml), median (IQR)	175 (0–850)	75 (0–833)	−1.352	.176	75 (0–833)	150 (0–875)	0.000	1.000
UF/day (ml), median (IQR)	805 (133–1055)	700 (431–1082)	−1.258	.208	700 (431–1082)	825 (184–1262)	−0.691	.490
Overhydration (l)	2.8 ± 1.3	2.3 ± 1.5	2.456	.032	2.6 ± 1.5	3.2 ± 1.9	−2.235	.047
Systolic BP (mmHg)	126 ± 14	123 ± 18	0.634	.537	125 ± 13	121 ± 14	0.780	.449
Diastolic BP (mmHg)	80 ± 11	81 ± 13	−0.020	.984	79 ± 11	77 ± 7	0.880	.395
Haemoglobin (g/l)	118.1 ± 9.1	117.6 ± 8.7	0.293	.774	116.6 ± 5.7	118.0 ± 5.7	−0.733	.476
Albumin (g/l)	38.6 ± 3.4	38.7 ± 3.4	−0.248	.808	37.8 ± 3.8	38.1 ± 3.5	−0.402	.694
Urea (mmol/l)	19.6 ± 5.1	22.8 ± 5.8	−2.745	.017	21.7 ± 6.9	19.2 ± 5.0	2.278	.040
Creatinine (μmol/l)	985 ± 254	1157 ± 381	−3.841	.002	1083 ± 405	999 ± 276	1.732	.107
Uric acid (μmol/l)	356 ± 90	376 ± 83	−0.795	.441	347 ± 95	344 ± 88	0.184	.857
Calcium (mmol/l)	2.35 ± 0.14	2.34 ± 0.12	0.748	.468	2.32 ± 0.13	2.33 ± 0.12	−0.048	.962
Phosphate (mmol/l)	1.38 ± 0.25	1.71 ± 0.37	−3.784	.002	1.60 ± 0.38	1.41 ± 0.32	2.215	.045
Potassium (mmol/l)	4.22 ± 0.44	4.61 ± 0.45	−2.876	.013	4.59 ± 0.54	4.20 ± 0.51	2.353	.035
Sodium (mmol/l)	138.5 ± 3.4	138.1 ± 2.5	0.566	.581	137.9 ± 2.4	138.1 ± 3.5	−0.280	.784
Bicarbonate (mmol/l)	27.4 ± 2.4	25.2 ± 3.1	2.564	.024	27.0 ± 2.8	26.8 ± 2.9	0.280	.784
Weekly total Kt/V	1.77 ± 0.25	1.70 ± 0.35	1.075	.302	1.71 ± 0.36	1.75 ± 0.31	−0.516	.615
Weekly renal Kt/V, median (IQR)	0.14 (0–0.57)	0.07 (0–0.47)	−1.521	.128	0.07 (0–0.40)	0.04 (0–0.45)	−0.954	.340
Creatinine clearance rate (l/week)	56.8 ± 13.1	50.0 ± 12.1	2.917	.012	49.7 ± 11.8	53.6 ± 12.9	−2.130	.053
Renal creatinine clearance rate (l/week), median (IQR)	6.1 (0–28.2)	3.2 (0–21.4)	−1.400	.161	3.24 (0–21.0)	1.6 (0–21.2)	−0.507	.612
High-sensitivity C-reactive protein (mg/l), median (IQR)	1.28 (0.46–4.42)	1.70 (0.96–4.31)	−1.256	.209	2.65 (0.81–6.57)	1.70 (0.82–4.00)	−0.175	.861

Values are presented as mean ± SD unless stated otherwise.

Table 4: Changes in parameters in dialysis effluent before and after IPD and CAPD.

	IPD				CAPD			
Parameters	Before	After	Z/t	P-value	Before	After	Z/t	P-value
IL-6 (pg/ml), median (IQR)	19.1 (8.8–23.1)	16.1 (7.6–27.1)	−0.722	.470	15.4 (7.6, 30.0)	17.9 (11.0, 35.8)	−1.915	.056
VEGF (pg/ml), mean ± SD	35.4 ± 25.2	35.7 ± 22.4	−0.032	.975	38.2 ± 24.1	40.3 ± 18.9	−0.350	.732

from original CAPD to nightly IPD or daily IPD). This study reveals that short-term peritoneal rest can achieve effects comparable to those observed with peritoneal rest lasting several days or even months. Specifically, it reduces high PSTR, increases UF volume and improves the patient's volume status. However, this dialysis method has its disadvantages. With the reduction in daily dialysis time, the removal of toxins is inevitably diminished, necessitating close monitoring of biochemical indicators such as urea, potassium and phosphorus. Consequently, the author posits that CAPD and nocturnal IPD or daily IPD can be utilized interchangeably in clinical practice, allowing each method to benefit from the strengths of the other.

In this study, no changes in inflammatory indicators or neovascularization markers were observed in relation to the underlying mechanism. This lack of change may be attributed to the small sample size.

The main limitation of this study is the absence of a washout period when the two treatment methods were switched. This lack of a washout period may introduce confounding variables that could impact the changes observed before and after CAPD. Nevertheless, the changes observed before and after IPD were not influenced and the primary findings of the study remained unaffected.

CONCLUSION

This randomized controlled crossover clinical trial presents preliminary findings indicating that in PD patients with high peritoneal transport and high average transport, a 4-week period of short-term peritoneal rest by switching from CAPD to IPD (without long dwell) can lead to reductions in PSTRs and increases in UF volumes, while maintaining clinical safety. However, it is still necessary to closely monitor a range of toxins and electrolyte levels.

FUNDING

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AUTHORS' CONTRIBUTIONS

B.W. conceived and designed the experiments, analysed the data and wrote the paper. H.Z. contributed to the writing of the manuscript, provided critical revisions and agreed to be accountable for the content of the work. L.Z. contributed reagents/materials. A.L., L.L., J.Q., X.C., C.M. and Y.H. performed the PET.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

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