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Effect of central dialysis fluid delivery system on markers of inflammation in hemodialysis patients

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Abstract

Background The utilization of ultrapure dialysate has been shown to decrease dialysate contamination and mitigate inflammatory responses. The central dialysate delivery system (CDDS) has the potential to attain a level of purity similar to ultrapure dialysate. Nevertheless, there is limited research examining the impact of CDDS on inflammation in comparison to single-patient dialysis fluid delivery system(SPDDS). This study aims to investigate the effects of CDDS utilizing ultrapure dialysate on ameliorating the microinflammatory state in hemodialysis patients.

Method A retrospective cohort clinical study enrolled a total of 125 hemodialysis patients, with 58 patients from the CDDS unit and 67 patients from the SPDDS unit. Each participant was monitored for a period of 6 months, and the repeated measurement data was analyzed using a generalized linear mixed models (GLMM).

Results The average age of the studty cohort was 56.22 ± 12.64 years. The GLMM analysis showed a significant time*group interaction effect on hs-CRP changes over the follow-up period (β = -1.966, $F_{Time*\ CDDS\ group} = 13.389$, $P < 0.001$). A linear mixed model analysis with random slope showed that a different slope was observed between CDDS group and SPDDS group (β_{CDDS} =—0.793; $\beta_{SPDDS} = 0.791$), indicating a decreased hs-CRP levels in CDDS group, while increased in the SPDDS group over the follow-up period. However, no significant time*group interaction effect were observed on albumin and β_2-microglobulin levels during follow-up period(β_2-microglobulin: β = -0.658, $F_{Time*\ CDDS\ group} = 1.228$, $P = 0.269$; albumin: β = 0.012, $F_{Time*\ CDDS\ group} = 1.429$, $P = 0.233$).

Conclusion Using ultrapure dialysate in the CDDS is associated with an improvement in hs-CRP levels compared to standard dialysate, which might confer long-term clinical advantages.

Keywords Maintenance hemodialysis, Ultrapure dialysate, Central Dialysate Delivery system, CDDS, Inflammation

Introduction

Although kidney transplantation offers improved survival rates compared to dialysis, maintenance hemodialysis (MHD) remains the primary treatment modality for end-stage kidney disease patients due to the limited availability of donor kidneys. It is relatively safe, effective, and widely used in clinical treatment [1]. However, microinflammatory state is common in MHD patients, which is related to atherosclerosis, anemia and malnutrition, ultimately contributing to higher mortality in MHD

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patients [2]. Microinflammation is primarily characterized by alterations acute phase proteins(plasma C reactive protein, fibrinogen, and serum amyloid protein) and proinflammatory cytokine activation such as interleukin (IL) and tumor necrosis factor-α (TNF-α). Among these factors, hypersensitivity C-reactive protein (hs-CRP) is the most reliable, precise and acknowledged inflammatory biomarker. Prior research has shown that plasma concentrations of hs-CRP serve as predictors of microinflammation.

The causes of microinflammation are closely related to many factors, including accumulation of advanced glycation end products, oxidative stress, uremia toxins, types of dialysis membranes, dialysis technology and quality [3, 4]. The speculation that exposure of blood to dialysate is a potential cause of chronic inflammation in addition to uremia itself has recently received considerable attention. Previous studies have showed that the purity of the dialysate and the permeability of the dialyzer to bacterial soluble products might contribute to some of the the complications of dialysis, including malnutrition inflammation-atherosclerosis syndrome and accelerated cardiovascular morbidity [5, 6]. In vitro studies have shown that cytokines production by peripheral white blood cells was influenced by the levels of endotoxin contamination in the dialysate compartment and the permeability of the dialyzer membrane [7].

Studies indicated that inadequate dialysis or impure dialysate in hemodialysis (HD) patients played a significant role in the development of microinflammatory state. Ultrapure dialysate has been shown to mitigate dialysate contamination and alleviate inflammatory responses [8]. There are three types of available dialysis fluid delivery systems globally: the single-patient dialysis fluid delivery system(SPDDS), the central concentrates delivery system (CCDS), and the central dialysate delivery system (CDDS). In the SPDDS system, purified reverse osmosis (RO) water was distributed to individual HD machines with two separate buckets containing acid and bicarbonate concentrates. In CCDS system, acid fluid and bicarbonate concentrates were central distributed to individual HD machines separately. The CDDS system requires a single stream as a result of the centralized delivery of a fully proportioned dialysate fluid, which consists of a mixture of dialysis fluid, acid and bicarbonate concentrates, and diluted RO water. The CDDS system is basically comprised of a water treatment system, a powder dialysate mixing unit, a central dialysate proportioning unit, bedside consoles, and a fluid distribution piping system that interconnects these components together. This system integrates the processes involved in preparing and conveying dialysis water, ultimately achieving a degree of purity comparable to ultrapure dialysate [9]. Several studies have demonstrated that improving the purity of dialysate can decrease the micro-inflammatory state in hemodialysis patients [10]. However, there was few evidence to investigate the impact of CDDS on hs-CRP compared to single-patients system over time.

This study explores the effect of ultrapure dialysate produced by the CDDS on improving the microinflammatory state of hemodialysis patients, aiming to provide novel approaches for clinical practice.

Materials and methods

Participants

This retrospective cohort clinical study was designed at the Department of Blood Purification Center of Changzhou First People Hospital from 2019 to 2023. The study protocol has been registered on the Chinese Clinical Trial Registry (ChiCTR) (https://www.chictr.org.cn/; registration number ChiCTR2400086948). Hemodialysis patients initially received treatment with SPDDS on the 5th floor until 2019. Subsequently, following the implementation of CDDS in 2019, a portion of patients were relocated to the 7th floor for CDDS treatment. Patients in CDDS unit were treated with ultrapure dialysate (UPD), which was defined as liquid with endotoxin levels < 0.03 endotoxins units (EU)/ml and sterile culture < 0.1 colony forming units (CFU)/ml (ISO 11663–2014). However, patients in SPDDS unit used standard dialysate, which was defined as liquid with endotoxin levels < 0.25 EU/ml and sterile culture < 50 CFU/ml (ISO 11663–2014). It was worth noting that the replacement fluid employed for hemodiafiltration met the criteria of ultrapure dialysate, because there are two additional bacterial filters in the dialysis machine.

The criteria for patient inclusion were: age 18 to 90 years; patients undergoing maintenance hemodialysis three times weekly for more than one months; patients with white blood cell count $\geq 4.0 \times 10^9$/L and PLT $\geq 100.0 \times 10^9$/L for more than one month; and a willingness to participate in the study. The exclusion criteria were: a. chronic infections or active inflammatory diseases or acute infections, b. treatment with cytostatics, anti-inflammatory drugs or glucocorticoid (GC), c. chronic bleeding or haemolysis, major surgery in the 3 months prior to start of the study, d. patients with radiotherapy or active cancer, e. patients with severe liver impairment, active autoimmune disease, active hepatitis, syphilis or acquired immune deficiency syndrome (AIDS). Abandonment criteria were: voluntary decision by the patient, reception of a renal transplant or death.

Study design and dialysis procedures

After the initial assessment and the application of inclusion and exclusion criteria, a total of 125 hemodialysis

patients were enrolled in the study, with 58 patients from the CDDS unit, and the other 67 patients from the SPDDS unit. No exchange of patients was carried out between the two units during the study, and each participant was followed for 6 months. Routine patient care was performed according to national and international Quality of Care Guidelilnes.

The treatment duration was standardized to 4 h during the follow-up period for both groups. Hemodialysis patterns in the two groups consisted of two hemodialysis (HD) and one hemodiafiltratin (HDF) peer week. HDF was performed in the postdilution mode, with synthetic high-flux polyethersulfone dialyzers (SM180H (Sansin, China)). Hemodialysis patients were treated with synthetic high-flux dialyzers (SM160H (Sansin,China)). The same water treatment system (Lauer, Germany) was used in both groups. However, HD machines were different between the two groups (JMS GC-110N (Japan) in CDDS group; Braun (Germany) in SPDDS group).

Data collection

At baseline, standardized forms used to collect clinical laboratory, and treatment-related data. The main variables related to the inflammation studied were: hs-CRP (with a minimum quantification limit of 0.499 mg/l), albumin (ALB), and β_2-microglobulin (β_2—MG), which were measured quarterly. The repeated measurements were taken at three time points: preoperative, 3 months postoperative, and at the final observation. Other variables analysed were: sex, age, dialysis vintage, comorbidity, etiology, vascular access, body mass index (BMI), single-pool KT/V (spKT/V), hemoglobin (Hb), serum creatinine (Scr), calcium, phosphate, and parathyroid hormone (PTH), which were measured at baseline. SpKT/V [K: dialyzer clearance (ml/min); t: dialysis time (min); V: urea distribution volume (ml)] was developed by Frank Gotch and John Sargnt ans further equilibrated by Daugirdas in the 1990s; it indicated the primary indicator of dialysis adequacy. The spKT/V was measured using the single—pool Daugirdas formula $spKT/V = -1n((postBUN/preBUN) - 0.008 \times t) + [(4 - 3.5 \times (postBUN/preBUN)) \times UF/BW]$, in which postBUN represented postdialysis blood urea nitrogen, preBUN represented predialysis blood urea nitrogen, UF meant ultrafiltration, and BW meant body weight [11, 12].

Outcome

The outcome of this analysis was the changes of hs-CRP, albumin and β_2-microglobulin over time between the CDDS and SPDDS groups.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) (Gaussian distribution) or median (Q1-Q3) (Skewed distribution) for continuous variables and as numbers or categorical variables. A non-parametric Kruskal–Wallis' test (for Skewed distribution variables) were performed to calculate the differences in three different time points. Both Mann–Whitney U (for Skewed distribution) test and the chi-square test (for categorical variables) were used to access the differences in two groups. A time * group interaction effect on hs-CRP, ALB, and β2-MG changes over the follow-up period were analyzed using a generalized linear mixed models (GLMM). Fixed effects included time, group, time × group, sex, age, dialysis vintage, and BMI, while individual differences served as variable effects. In the GLMM analysis, SPDDS group and female were used as reference group.

A linear mixed model (random slope model) was used to capture the intricate longitudinal changes in hs-CRP, ALB, and β2-MG across different groups over time. Statistical analysis was performed using IBM SPSS 26.0 and R 4.3, with a 5% level of statistical significance. The results are presented as means with 95% confidence intervals (CIs).

Results

Baseline characteristics of the study population

The baseline characteristics of the patients are depicted in Table 1. A total of 125 hemodialysis patients were included in this observational study, of whom 59.2% were males and 40.8% were females, with an average age of 56.22 ± 12.64 years old. The median dialysis vintage was 4 years (rang of 2–10 years). The etiology of end-stage renal disease (ESRD) for the study population was Chronic glomerulonephritis (67.2%), diabetic nephropathy (17.6%), polycystic kidney disease (6.4%), Benign hypertensive nephrosclerosis (3.2%), IgA nephropathy (2.4%), medullary sponge kidney (1.6%),ectopic kidney (0.8%) and Anca-associated vasculitis (0.8%). No significant differences were noted in sex, dialysis vintage, comorbidity, spKT/V, etiology, Hb, albumin, calcium, phosphate, parathyroid hormone, hs-CRP, age, except for β_2-microglobulin levels, between two groups. BMI and β_2-microglobulin levels were higher in SPDDS group ($P = 0.025$ for BMI; $P = 0.039$ for β_2-MG) (Table 1).

Effect of CDDS on hs-CRP

Baseline hs-CRP was 3.30 (1.04, 5.05) mg/l in the CDDS group and 2.40 (1.02, 5.00) mg/l in the SPDDS group. hs-CRP levels decreased significantly in CDDS patients

Table 1 Baseline characteristics of the patients

	Total ($n=125$)	CDDS ($n=58$)	SPDDS ($n=67$)	P
Male	59.2%	53.4%	64.2%	0.223
Age	56.22 ± 12.64	57.86 ± 12.65	54.79 ± 12.61	0.178
Dialysis vintage (years)	4 (2,10)	3.5 (2,10)	5 (2,10)	0.290
Comorbidity				
Hypertension	29.6%	29.3%	29.9%	0.947
Cardiac insufficiency	22.4%	29.3%	16.4%	0.085
BMI	22.12 ± 5.39	20.92 ± 6.16	23.16 ± 4.41	0.025
Etiology				0.053
Chronic glomerulonephritis	67.2%	58.6%	74.6%	
Diabetic nephropathy	17.6%	17.2%	17.9%	
Polycystic kidney	6.4%	10.3%	3.0%	
Benign hypertensive nephrosclerosis	3.2%	6.9%	0%	
Medullary sponge kidney	1.6%	3.4%	0%	
IgA nephropathy	2.4%	1.7%	3%	
Anca-associated vasculitis	0.8%	0%	1.5%	
Ectopic kidney	0.8%	1.7%	0.0%	
Vascular access				0.544
Arteriovenous fistula	89.6%	91.4%	88.1%	
Long-term central venous catheter	10.4%	8.6%	11.9%	
spKT/V	1.35 ± 0.26	1.35 ± 0.24	1.34 ± 0.27	0.887
Hemoglobin(g/L)	110(95, 118)	110.5(91.8, 118.3)	109(99, 118)	0.659
Albumin(g/L)	38.25(36.15,40.30)	38.35(35.48,40.33)	38.10(36.39,40.33)	0.886
Calcium(mmol/L)	2.25(2.14,2.36)	2.24(2.12,2.34)	2.26(2.14,2.38)	0.735
Phosphate(mmol/L)	1.85(1.56,2.33)	1.85(1.52,2.19)	1.83(1.61,2.40)	0.621
Parathyroid hormone(pg/ml)	283.4(129.7,505.2)	320.7(178.1,519.5)	207.2(93.7,485.5)	0.098
hs-CRP (mg/L)	2.60(1.04,5.00)	3.30(1.04, 5.05)	2.40 (1.02, 5.00)	0.113
β_2-microglobulin (mg/dl)	20.38(18.30,23.82)	19.90(17.66.21.63)	21.30(18.44,25.28)	0.039

hs-CRP high-sensitivity C-reactive protein, *CDDS* Central Dialysate Delivery System, *SPDDS* Single-Patient Dialysis fluid Delivery System, *spKT/V* single-pool KT/V

and increased significantly on SPDDS groups over time (all $P<0.05$) (Table 2 and Fig. 1).

A GLMM analysis was described in Table 3. The GLMM analysis was conducted taking into account the three factors including times (baseline, 3 months later, and final observation), group (CDDS and SPDDS groups), and the interaction between time and group, with confounding factors such as sex, age, dialysis vintage, and BMI as fixed effects and individual as a random effect. In the GLMM analysis, SPDDS group were used as reference group. As Table 3 shown, there was a significant time*group interaction effect on hs-CRP changes over the follow-up period ($\beta=$-1.966, $F_{Time*CDDS\ group}=13.389$, $P<0.001$), indicating that for every unit increase in time, the CDDS group showed a significantly decrease in hs-CRP level compared to the SPDDS group (an additional decrease of 1.966) (Table 3 and Fig. 1).

Additionaly, In GLMM analysis adjusted for various confounders, patients with older age, and higher BMI were significantly associated with higher hs-CRP(age: $\beta=0.079$, $P<0.001$; BMI: $\beta=0.160$, $P=0.003$).

In linear mixed model analysis which used random slope model, group factor was used as random effects, and time factor as fixed effects. A different slope was observed between CDDS group and SPDDS group ($\beta_{CDDS}=$—0.793; $\beta_{SPDDS}=0.791$), indicating that a decreased hs-CRP levels in CDDS group, while increased in the SPDDS group over the follow-up period (Fig. 2).

Effect of CDDS on albumin

Baseline albumin was 38.3 (35.4, 39.8) mg/l in the CDDS group and 38.3 (36.3, 40.4) mg/l in the SPDDS group. No significant differences were found between the two groups(all $P>0.05$) (Table 1).

In GLMM analysis adjusted for various confounders, patients with older age and shorter dialysis vintage were significantly associated with lower albumin (age: $\beta=$—0.003, $P<0.001$; dialysis vintage: $\beta=0.004$, $P=0.008$) (Table 3). However, no significant time*group

Table 2 Changes of CRP, ALB and β2-MG during follow-up period

	T1	T2	T3	P[a]
hs-CRP (mg/L)				
CDDS	3.30(1.04, 5.05)	2.60(0.96,5.00)	2.00(0.90,39.40)	0.030
SPDDS	2.40 (1.02, 5.00)	3.30(2.12,6.08)	4.17(2.53,5.08)	0.020
P[b]	0.113	0.037	< 0.001	
ALB (g/L)				
CDDS	38.35(35.48,40.33)	38.30(36.65,40.35)	38.15(36.63,39.40)	0.663
SPDDS	38.10(36.30,40.33)	38.20(35.13,40.48)	37.70(35.70,40.70)	0.978
P[b]	0.886	0.639	0.998	
β_2-MG (mg/dl)				
CDDS	19.91(17.66.21.63)	18.95(16.77,22.88)	20.07(17.40,21.62)	0.655
SPDDS	21.30(18.44,25.28)	20.61(18.39,24.19)	20.89(18.55,25.28)	0.648
P[b]	0.039	0.060	0.050	

P[a] the results of non-parametric Kruskal–Wallis' test; *P[b]* the results of Mann–Whitney U test. *T0* baseline time point. *T1* time point of 3 months. *T2* time point of 6 months, *CDDS* Central Dialysate Delivery System, *SPDDS* Single-Patient Dialysis fluid Delivery System, *hs-CRP* high-sensitivity C-reactive protein, *ALB* Albumin, *β_2-MG* β_2-microglobulin

interaction effect was observed on ALB level changes over the follow-up period (β = 0.012, $F_{Time^* CDDS\ group} = 1.429$, $P = 0.233$), which suggested that there was no significant difference in the fluctuation of ALB levels between the CDDS and SPDSS group over time during the follow-up period (Fig. 1).

Effect of CDDS on β2—microglobulin

Baseline β_2—microglobulin was 19.90 (17.66, 21.63) mg/dl in the CDDS group and 21.30 (18.44, 25.28) mg/dl in the SPDDS group. No significant differences were noted over time in the two groups (all $P > 0.05$) (Table 2).

In GLMM analysis adjusted for various confounders, female, patients with longer dialysis vintage, and lower BMI significantly were associated with higher β_2—microglobulin level(male: β = -1.406, $P = 0.019$; dialysis vintage: β = 0.159, $P = 0.023$; BMI: β = -0.235, $P < 0.001$) (Table 3). However, no significant time*group interaction effect was observed on β_2-MG level changes over the follow-up period (β = -0.658, $F_{Time^* CDDS\ group} = 1.228$, $P = 0.269$), demonstrated a similar changes of β_2-MG levels between the CDDS and SPDSS group over time during the follow-up period (Fig. 1).

Discussion

The present study is the largest retrospective cohort study performed on the influence of dialysis fluid delivery systems on inflammation markers in patients undergoing prevalent hemodialysis. A significant time*group interaction effect on hs-CRP changes was obeserved over the follow-up period. The hs-CRP level in patients with CDDS statistically reduced gradually, while those in SPDDS group increased through 6-month follow-up. In addition, β_2-microglobulin level in CDDS group was lower than SPDDS group during the whole follow-up period. However, no significant time*group interaction effect were observed on albumin and β_2-microglobulin levels during follow-up period.

Patients with uremia have a micro-inflammatory state, which is different from microbial infections. Several factors, including the microbiological quality of the

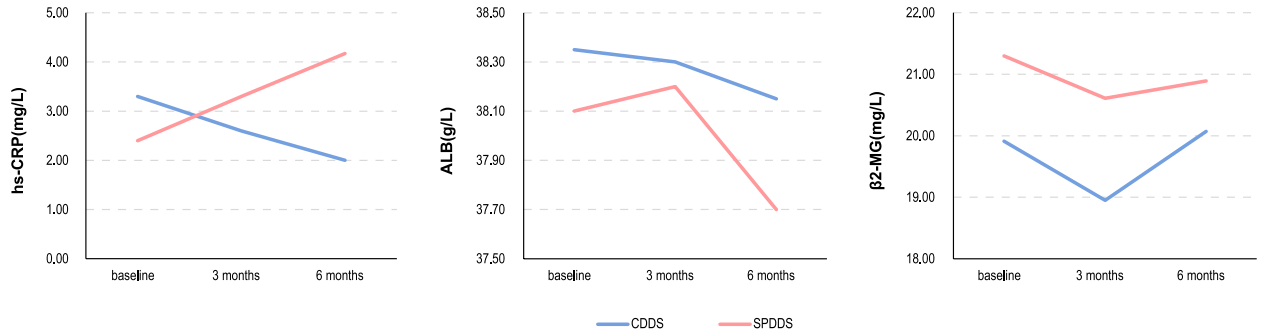

Fig. 1 The median value of hs-CRP, ALB, and β2-microglobulin for both groups during the follow-up period. **A** hs-CRP throughout the follow-up period. **B** ALB throughout the follow-up period. **C** β2-microglobulin throughout the follow-up period

Table 3 Fixed Effect Results of GLMM Model for hs-CRP, ALB, and β_2-MG

					95% CI	
	Source	**Coefficient**	**F**	**P**	**Lower**	**Upper**
hs-CRP	Corrected model	-5.645	5.317	<0.001	-9.797	-1.493
	CDDS group	2.191	4.705	0.031	0.203	4.179
	time	1.198	0.642	0.424	0.499	1.897
	sex	0.305	0.284	0.594	-0.822	1.432
	age	0.079	12.695	<0.001	0.035	0.122
	Dialysis vintage	-0.011	0.027	0.869	-0.143	0.121
	BMI	0.160	9.096	0.003	0.056	0.265
	time * CDDS group	-1.966	13.389	<0.001	-3.023	-0.908
ALB	Corrected model	3.747	4.386	<0.001	3.645	3.849
	CDDS group	0.004	0.035	0.852	-0.039	0.047
	time	-0.009	0.383	0.536	-0.022	0.005
	sex	0.008	0.314	0.575	-0.020	0.036
	age	-0.003	22.159	<0.001	-0.004	-0.001
	Dialysis vintage	0.004	7.178	0.008	0.001	0.008
	BMI	0.000	0.033	0.856	-0.002	0.003
	time * CDDS group	0.012	1.429	0.233	-0.007	0.031
β2-MG	Corrected model	24.931	7.804	<0.001	20.470	29.392
	CDDS group	-1.123	1.036	0.310	-3.297	1.050
	time	0.742	1.938	0.165	-0.062	1.547
	sex	-1.406	5.562	0.019	-2.579	-0.232
	age	0.015	0.405	0.525	-0.032	0.063
	Dialysis vintage	0.159	5.213	0.023	0.022	0.296
	BMI	-0.235	16.633	<0.001	-0.348	-0.121
	time * CDDS group	-0.658	1.228	0.269	-1.827	0.511

The analysis was performed using a generalized linear mixed model. Fixed effects included time, group, time × group, sex, age, dialysis vintage, and BMI. Individual differences served as variable effects. And SPDDS group and female were used as reference group.*β_2-MG*β_2-microglobulin, *BMI*body mass index, *ALB*albumin,*hs-CRP*high-sensitivity C-reactive protein, *CDDS*Central Dialysate Delivery System

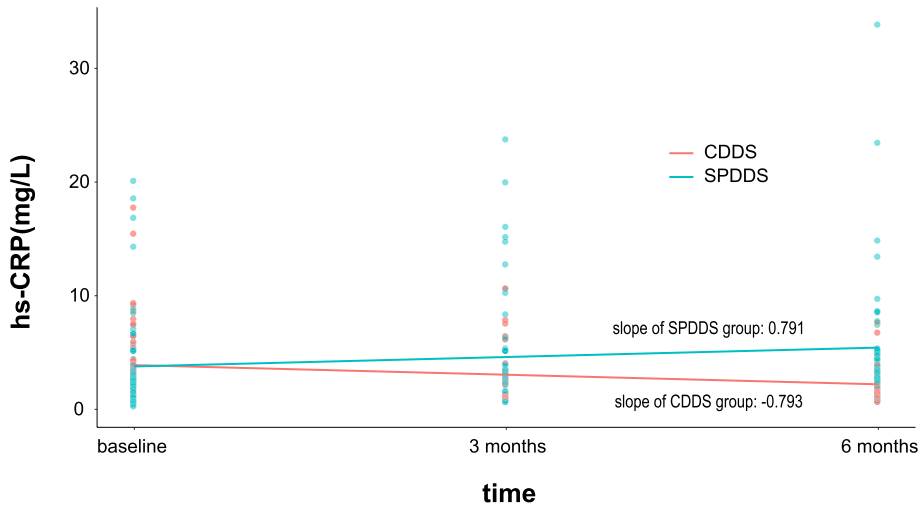

Fig. 2 Trajectory Plot of Two Groups by Linear Mixed Models with Random Slopes

dialysate, vascular access, membrane bioincompatibility, retention of uremic toxins, infection, poor nutritional status, and comorbidities, have been proposed as potential contributors to the sustained micro-inflammatory state in HD patients. Previous study has reported that a concentration of 0.5 EU/mL of endotoxin molecules could stimulate monocytes to produce pro-inflammatory cytokines such as IL-6 and tumor necrosis factor- α, which played crucial roles as mediators of acute or chronic inflammation in HD patients [13, 14]. A study demonstrated that ultrapure dialysis fluid decreased endotoxin levels, reducing inflammation and potentially preventing complications includinig atherosclerosis, malnutrition, erythropoietin resistance, dialysis-related amyloidosis, and other complications in dialysis patients [15]. It has been well documented that dialysate with lower endotoxin contamination was associated with lower levels of proinflammatory cytokines, CRP and oxidative stress markers [16, 17]. Therefore, improving the purity of dialysate is crucial for reducing microinflammation. Ultrapure dialysate must meet the Japanese Society for Dialysis Therapy (JSDT) standards, with Bacteria < 0.1 CFU/ml and ET < 0.001 EU/ml [18]. In order to attain ultrapure dialysis, a comprehensive dialysis system must be utilized. The Central Dialysate Delivery System (CDDS) offers cost-effectiveness, automation, multi-level endotoxin filtration, and disinfection without dead space in the preparation and delivery of ultrapure dialysate. So it ensures safe and stable endotoxin levels at 0.001 EU/ml for patients [19].

In our study, a reduction in hs-CRP levels was observed following the purification of dialysate. Consistent with our results, a study conducted by Hassan MS et al. showed that ultrapure dialysate produced by the CDDS was positively reflected in minimizing the inflammatory status of patients [20]. A meta-analysis involved 31 studies showed that use of ultrapure dialysate in hemodialysis patients resulted in a decrease in CRP level [21]. Regrettably, data on IL-6 and tumor necrosis factor- α were not available because they were not routinely assessed in our hospital.

Albumin levels have a distinct place amongst the routine blood investigations performed in maintenance hemodialysis patients. Albumin is a sensitive indicator of future mortality in dialysis patients [22]. In the meantime, hypoalbuminemia is the most widely studied biomarker among dialysis patients in terms of nutritional parameters [23]. A meta-analysis by Paweena et al. [24] found that ultrapure dialysate significantly increased albumin level, which was contradicted with our study. The present study showed no significant difference in albumin levels between the two groups. This can be explained by the fact that serum albumin level was not a sensitive marker to be changed by these two different dialysate systems, and it could be increased by oral nutritional supplements or appetite stimulants [25, 26].

β_2-MG is a medium macromolecular globulin produced by platelets, lymphocytes and polykaryotic leukocytes, which is freely excreted from the kidneys through the glomerular filtration barrier [27]. It's also a commonly used marker of kidney damage in the clinic. When renal function is damaged, its filtration effect is significantly reduced [28]. The production rate of β_2-MG is constant, but it is increased in inflammation, infection and lymphoproliferative diseases [29]. Its accumulation in the human body can lead to amyloidosis. Dialysis-associated amyloidosis (DRA) is a systemic amyloidosis associated with osteoarticular lesions, including carpal tunnel syndrome (CTS), trigger finger (TF), spinal canal stenosis (SCS), destructive spondyloarthropathy (DSA), joint arthropathy, and bone cysts [30, 31]. As for tissue damage caused by β_2-MG deposition, it has been reported that advanced glycation end-products and advanced oxidation protein products located on β_2-MG in uremic states can induce proinflammatory effects, which are thought to be triggered by bioincompatible dialysis and contaminated dialysate [29]. In the past two decades, although the reduction of β_2-MG level has not reached the ideal level, the improvement of HD technology has undoubtedly contributed to delaying the onset of DRA and reducing its incidence and prevalence. Ultrapure dialysate is one of the important methods [17]. Ryuichi Furuya et al. found that ultrapure dialysate reduced the content of β_2-MG in the serum of hemodialysis patients [30], which was in concordance with our result. Our study showed that the β_2-MG level was lower in CDDS group than SPDDS group.

This study has some limitations. First, this was a single-center observational study with a relatively small sample size, which might have led to unavoidable selection bias. Second, inflammation was assessed only by CRP levels, not by other inflammation markers, such as IL-6 and TNF-α, which were not routinely measured in our hospital. Finally, the follow-up period was relatively short. Further prospective, larger multicenter clinical trials with longer follow-up periods are required to confirm this finding.

Conclusion

In conclusion, the present study showed that the use of ultrapure dialysate in CDDS group is associated with an improvement in hs-CRP levels compared to standard dialysate in SPDDS group, which might confer long-term clinical benefits.

Abbreviations

CDDS	Central dialysate delivery system
MHD	Maintenance hemodialysis
HD	Hemodialysis

CCDS	Central concentrates delivery system
RO	Reverse osmosis
hs-CRP	Hypersensitive C-reactive protein
SPDDS	Single-patient dialysis fluid delivery system
UPD	Ultrapure dialysate
GC	Glucocorticoid
AIDS	Acquired immune deficiency syndrome
HDF	Hemodiafiltratin
BMI	Body mass index
ALB	Albumin
β_2 – MG	β_2-Microglobulin
spKT/V	Single-pool KT/V
Hb	Hemoglobin
Scr	Serum creatinine
PTH	Parathyroid hormone
GLMM	Generalized linear mixed models
ESRD	End-stage renal disease
JSDT	Japanese Society for Dialysis Therapy
DRA	Dialysis-associated amyloidosis
CTS	Carpal tunnel syndrome
TF	Trigger finger
SCS	Spinal canal stenosis

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Authors' contributions
Yanhong Ni, Wenhui Wu, Hua Zhou and Min Yang were responsible for the study design. Min Li, Xiying Zhu, Hongyan Niu, Jinfeng Liu, Lina Xue and Yeqian Liu contributed to collecting data. Wenhui Wu, Min Li and Min Yang analyzed data. Yanhong Ni completed the manuscript writing. Min Yang reviewed the manuscript. The authors read and approved the fnalmanuscript.

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Availability of data and materials
The datasets used and analyzed during the study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Changzhou First People's Hospital (approval no. (2022) CL05-01 in accordance with the Declaration of Helsinki. Written informed consent for participation was obtained from each participant after full disclosure of the study aim. The researcher assured the participants that their information would be confidential.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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