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Original Article

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The Effect of Ultrapure Dialysate on Clinical Outcomes and Mortality During One Year Follow-up in Patients Undergoing Hemodialysis Treatment

İbrahim Doğan[1], Nur Ünal Kaya[2], Hüseyin Kayadibi[3]

[1]Department of Nephrology, Hitit University School of Medicine, Çorum, Turkey
[2]Department of Hemodialysis, Hitit University School of Medicine, Çorum, Turkey
[3]Department of Medical Biochemistry, Hitit University School of Medicine, Çorum, Turkey

Abstract

Objective: We investigated the relationship between mortality and clinical status in patients with hemodialysis using ultrapure dialysate and standard dialysate.
Materials and Methods: The study included 81 patients using ultrapure dialysate (Group 1) and 72 patients using standard dialysate (Group 2). Mortality rates, anemia, phosphorus, albumin, parathormone, and C-reactive protein (CRP) values were calculated as 1-year averages. Factors affecting mortality were evaluated by logistic regression analysis.
Results: In Group 1, potassium, phosphorus, uric acid, CRP, and hemoglobin levels were significantly higher (p<0.001, p=0.023, p=0.010, p=0.003, p<0.001, respectively), and transferrin saturation, ferritin, and HCO3− levels were significantly lower (p=0.007, p<0.001, p=0.001, respectively) than Group 2. The erythropoietin-stimulating agent's usage dose of Group 1 was 0.60 (0.11-1.00) µg/kg/month and 1.30 (0.80-2.17) µg/kg/month in Group 2 (p<0.001). Iron usage doses of Group 1 and Group 2 were 800 (425-1,275) mg/year and 1,300 (750-2,000) mg/year, respectively (p=0.002). There was no significant difference in mortality rates for the 1-year follow-up period (mortality rate in 12 patients [14.8%] in Group 1, 6 patients in Group 2 [8.9%], p=0.214). In the univariate and multivariate logistic regression analyses, age, serum Na, total protein, and CRP levels were found to be independent variables to determine mortality.
Conclusion: After 1 year of short-term follow-up, Group 1 had better anemia control than Group 2 but no positive effect on mortality.
Keywords: Chronic kidney disease, hemodialysis, mortality

Corresponding Author: İbrahim Doğan ✉ dr.ibrahimdogan@hotmail.com
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INTRODUCTION

The purity of the dialysate fluid has vital importance for patients undergoing hemodialysis (HD) (1). During HD sessions, the patient's blood comes in contact with 90 to 190 L of dialysate through the dialysis membrane. It is important to decrease the maximum limit of bacterial and endotoxin levels of dialysate (2). For standard dialysate fluid purity, the maximum bacterial contamination of <100 colony forming units (CFU)/mL and endotoxin levels of <0.25 endotoxin units (EU)/mL are defined. According to the Association for the Advancement of Medical Instrumentation standards, ultrapure dialysate recommended for HD is defined as having <0.1 CFU/mL bacterial content and <0.03 EU/mL endotoxin content (3).

Serological findings of inflammation may reach rates of 30 to 50% among patients undergoing HD (4). The circulating microbial products and endotoxemia contribute to the systemic inflammatory status (5). In addition, disrupted antioxidant system was observed owing to the presence of endotoxins in patients undergoing HD (6).

The circulating endotoxin levels in patients undergoing HD are associated with arterial stiffness and systemic inflammation, and it was shown that endotoxin levels reduced with the use of ultrapure dialysate (1). It has been shown that medium to large molecular weight uremic toxins, which are closely associated with cardiovascular disease and mortality, are more efficiently cleared with ultrapure dialysis (7). In patients dialyzed with ultrapure dialysate, less common inflammation, improved clinical outcomes, and better nutritional status were found (8, 9). Malnutrition-inflammation-atherosclerosis syndrome, dialysis-related amyloidosis, erythropoietin sensitivity, and increased cardiovascular morbidity were shown to reduce with the increase in HD fluid purity (10-12).

Lederer et al. (13) showed that ultrapure dialysis fluid decreased the cardiovascular morbidity by avoiding/reducing the chronic microinflammation. Canaud et al. (14) observed that the utility of ultrapure dialysate had a beneficial impact on mortality. Asci et al. revealed that there was no difference in mortality between the patients receiving ultrapure and standard dialysate treatments during the 3-year follow-up period. According to posthoc analyses, ultrapure dialysate treatment was related with a lower risk for cardiovascular diseases among subjects with at least 3 years of HD (15). Although the usage of ultrapure dialysate is shown to have important effects, such as improving inflammation, amyloidosis, and clinical symptoms, the correlation between the use of ultrapure dialysate and mortality is still controversial. Moreover, there are no large randomized controlled trials in the literature dealing with the effect of standard and ultrapure dialysates on mortality.

We aimed to investigate the relationship between the use of ultrapure and standard dialysates and mortality in patients undergoing HD.

MATERIALS AND METHODS

The study was approved by the Local Ethics Committee of Hitit University (29.01.2019; 2019-37), and written informed consent was obtained from the participants. Two centers using ultrapure dialysate and five centers using standard dialysate were included in the study. One-year averages of patients' data between April 2017 and April 2018 were included in the study.

The study included 81 patients with HD treatment using ultrapure dialysate for at least 1 year, and 72 age- and gender-matched patients with HD treatment using normal dialysate for the same period. Smoking status and HD therapy period were recorded. Patients received standard HD therapy with HCO_3^- (Na: 138-140 mmol/L, K: 1.5 mmol/L, Ca: 1.25-1.50 mmol/L, HCO_3^-: 32-35 mmol/L, and medium flux dialyzer: 1.4-2.1 m^2) for 4 hours three times a week, with a blood flow rate of 300 to 400 mL/min and dialysate flow rate of 500 mL/min. Body mass index (BMI) was calculated by the following formula: body weight (kg)/height^2 (m^2).

Main Points

- The use of ultrapure dialysate may not be superior to conventional purity dialysate in terms of mortality and dialysis sufficiency.
- The use of ultrapure dialysate may be more advantageous in terms of malnutrition.
- The use of ultrapure dialysate provided better anemia control in patients undergoing hemodialysis.

Arteriovenous fistula (AVF) was the only HD access route, patients with AVF grafts and catheters were not included in the study. Furthermore, patients with chronic liver disease, acute coronary events, acute cerebrovascular events, peripheral artery disease, stage 3-4 heart failure, trauma, burns, and acute infection were excluded from the study.

Patients received the following concurrent medications: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), aldosterone antagonists, calcium channel blockers, α and β blockers, nitrates, statins, antiphosphates, erythropoietin, darbepoetin, vitamin D, cinacalcet, anticoagulants, and antidiabetics.

Laboratory Analysis

Blood samples were collected from the antecubital vein in the morning of predialysis after fasting for 12 hours. The samples were centrifuged at 4,000 rpm for 5 minutes, and used to analyze sodium, potassium, calcium, phosphorus, glucose, blood urea nitrogen, creatinine, uric acid, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, albumin, total protein, parathormone (PTH), ferritin, transferrin saturation, and C-reactive protein (CRP) levels. Hemoglobin concentration was determined by complete blood count analyzer, and HCO_3^- level was measured by bood gas analyzer. Monthly single pool Kt/V (spKt/V) rates of patients were calculated. The 1-year spKt/V average was calculated. Mortality rates of patients were determined for 1 year.

Statistical Analysis

IBM Statistical Package for the Social Sciences 21.0 version (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analyses. Normal distribution of variables was analyzed using the Shapiro-Wilk test. The normally distributed variables are presented as mean±standard deviation, whereas the variables not distributed normally are presented as median (25^{th}-75^{th} inter quartile range). For normally distributed variables, comparisons between the two independent groups were performed using the Student t-test. For the variables not distributed normally, comparison between the two groups was performed using the Mann-Whitney U test. Categoric variables were compared using the Chi-square test. Factors affecting mortality were evaluated using univariate and multivariate logistic regression analyses. All reported p values were two-tailed, and those less than 0.05 were considered to be statistically significant.

RESULTS

The study included 81 patients using ultrapure dialysate (Group 1, median age 62 [50-70] years) and 72 patients using standard dialysate (Group 2, median age 60 [46-68] years). Patients in the Group 1 had higher BMI and use of β blocker medication (p=0.001 and p<0.001, respectively), and lower rates of cinacalcet use and chronic obstructive pulmonary disease (p<0.001 and p=0.043, respectively) than those in Group 2 (Table 1).

The erythropoietin-stimulating agents (ESA) usage dose for the Group 1 was 0.60 (0.11-1.00) μg/kg/month and 1.30 (0.80-2.17) μg/kg/month in the Group 2 (p<0.001). Iron usage doses of Group 1 and 2 were 800 (425-1275) mg/year and 1300 (750-2000) mg/year, respectively (p=0.002) (Table 1).

In terms of 1-year mortality rates, there were no significant differences (mortality owing to any cause during 1-year follow-up: 12 patients in Group 1 (14.8%) and 6 patients in Group 2 (8.9%), (p=0.214) (Table 1).

The 1-year mean biochemical and hormonal values were compared between the groups. The Group 1 had higher potassium, phosphorus, uric acid, CRP, and hemoglobin levels (p<0.001, p=0.023, p=0.010, p=0.003, and p<0.001, respectively), and lower transferrin saturation, ferritin, and HCO_3^- levels (p=0.007, p<0.001, and p=0.001, respectively) than Group 2. There were no statistically significant differences between the two groups for Ca, albumin, PTH, and spKt/V values (p=0.207, p=0.063, p=0.077, and p=0.537, respectively) (Table 2).

According to the univariate logistic regression analysis, age, serum Na, total protein, and CRP levels were independent variables for prediction of mortality, and according to the multivariate logistic regression analysis, age, serum Na, and total protein levels were independent variables for prediction of mortality. However, the use of ultrapure dialysate was not identified to affect mortality (Table 3, 4).

DISCUSSION

In our study, the use of ultrapure dialysate was identified to provide better anemia control during the 1-year follow-up in patients undergoing HD treatment. However, the use of ultrapure dialysate was not identified to have a positive effect on mortality.

Systemic inflammation has a key role in atherosclerosis (16) and is an important contributor to cardiovascular disease morbidity and mortality in patients with chronic kidney disease (17). In a retrospective cohort study including more than 130,000 pa-

Table 1. Demographic data, comorbid diseases, and drug usage of the study population

	Group 1 (n=81)	Group 2 (n=72)	p
Age (years)	62 (50-70)	60 (46-68)	0.254
BMI (kg/m^2)	26.9±5.2	24.1±4.7	0.001
Smoking (%)	11 (14)	15 (21)	0.233
HD duration (months) (%)	70 (38-104)	60 (39-91)	0.623
Water system duration (months)	57 (44-71)	60 (39-91)	0.399
Gender (F/M) (%)	35/46 (43/57)	31/41 (43/57)	0.985
HT (%)	59 (73)	50 (69)	0.643
DM (%)	31 (38)	20 (28)	0.169
CAD (%)	10 (12)	17 (24)	0.068
PD (%)	3 (4)	9 (13)	0.043
CVD (%)	0 (0)	2 (3)	-
PAD (%)	7 (9)	5 (7)	0.697
1.25 Vitamin D_3 (%)	57 (70)	44 (61)	0.227
Cinecalcet (%)	3 (4)	18 (25)	<0.001
Statin (%)	3 (4)	1 (1)	0.370
ACEi/ARB (%)	8 (10)	13 (18)	0.142
CCB (%)	26 (32)	22 (31)	0.837
BB (%)	41 (51)	16 (22)	<0.001
Mortality (%)	12 (14.8)	6 (8.3)	0.214
ESA (μg/kg/month)	0.60 (0.11-1.00)	1.30 (0.80-2.17)	<0.001
Iron (mg/year)	800 (425-1.275)	1.300 (750-2.000)	0.002

BMI: body mass index; HD: hemodialysis; F: female; M: male; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; PD: pulmonary diseases; CVD: cerebrovascular disease; PAD: peripheral artery disease; ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CCB: calcium channel blockers; BB: beta blockers; ESA: erythropoietin-stimulating agents

Table 2. Comparison of laboratory parameters in the groups

	Group 1 (n=81)	Group 2 (n=72)	p
BUN (mg/dL)	65 (58-72)	46 (37-60)	<0.001
Cr (mg/dL)	8.9±2.6	5.8±1.6	<0.001
Uric acid (mg/dL)	6.8±1.0	6.4±1.0	0.010
Na (mmol/L)	138 (137-140)	138 (137-139)	0.103
K (mmol/L)	5.2 (4.8-5.4)	4.4 (4.2-4.6)	<0.001
Calcium (mg/dL)	8.9 (8.5-9.3)	8.8 (8.4-9.3)	0.207
Phosphorus (mg/dL)	5.0 (4.6-5.3)	4.7 (4.1-5.2)	0.023
Total protein (g/dL)	7.1 (6.8-7.4)	7.0 (6.7-7.2)	0.037
Albumin (g/dL)	4.2 (3.9-4.3)	4.0 (3.8-4.2)	0.063
Total cholesterol (mg/dL)	155 (134-196)	165 (133-196)	0.694
LDL-C (mg/dL)	99 (84-125)	92 (66-116)	0.082
HDL-C (mg/dL)	34 (30-40)	37 (30-43)	0.228
Triglycerides (mg/dL)	151 (110-225)	153 (115-232)	0.533
Glucose (mg/dL)	106 (90-120)	107 (93-135)	0.345
CRP (mg/L)	7.7 (3.2-14.2)	3.9 (0.9-9.4)	0.003
WBC (10^9/L)	6.9 (5.7-8.1)	7.44 (5.8-9.5)	0.161
Hemoglobin (g/dL)	11.8 (11.3-12.4)	11.0 (10.5-11.6)	<0.001
Hematocrit (%)	36.3 (34.0-38.3)	32.7 (32.6-36)	<0.001
Transferrin saturation (%)	27 (22-33)	34 (24-38)	0.007
Ferritin (ng/mL)	576 (322-781)	966 (695-1.288)	<0.001
Bicarbonate	19.3 (18.5-20.2)	21.0 (19.0-22.0)	0.001
PTH (pg/mL)	348 (263-443)	412 (246-810)	0.077
spKt/V	1.5 (1.4-1.6)	1.5 (1.4-1.7)	0.537

BUN: blood urea nitrogen; Cr: creatinine; PTH: parathormone; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CRP: C-reactive protein; WBC: white blood cell

Table 3. Univariate logistic regression analysis for factors affecting mortality

	B	Walt	OR (95% CI)	p
Water system	-0.649	1.505	1.913 (0.679-5.393)	0.220
Age	0.077	8.348	1.080 (1.025-1.138)	0.004
Hemodialysis duration	0.009	2.868	1.009 (0.999-1.020)	0.090
Na	-0.245	5.188	0.783 (0.634-0.966)	0.023
Total protein	-1.607	6.443	0.200 (0.058-0.693)	0.011
CRP	0.027	7.162	1.027 (1.007-1.048)	0.007
Hemoglobin	-0.404	3.137	0.668 (0.427-1.044)	0.077
HT	-0.788	2.365	0.455 (0.166-1.242)	0.124
DM	0.275	0.282	1.316 (0.478-3.627)	0.595
CAD	-0.078	0.013	0.925 (0.248-3.448)	0.908

B: beta; CAD: coronary artery disease; CI: confidence interval; CRP: C-reactive protein; DM: diabetes mellitus, HT: hypertension; OR: odds ratio

tients receiving HD treatment three times per week in Japan, patients in centers with high dialysate endotoxin levels (≥0.1 EU/mL) were shown to have 28% higher mortality risk than patients from centers with low endotoxin levels (≤0.001 EU/mL) (18). The increased circulating endotoxin levels were related to the systemic inflammation that was responsible for vascular stiffness (1). The increase of water quality in patients with dialysis treatment is important to reduce the inflammation and to improve the survival (19).

Asci et al. (15) showed that ultrapure dialysate use had beneficial effects on the survival of patients undergoing dialysis

Table 4. Multivariate logistic regression analysis for factors affecting mortality

	B	Walt	OR (95% CI)	p
Water system	-1.356	3.462	0.258 (0.062-1.075)	0.063
Age	0.093	6.395	1.098 (1.021-1.180)	0.011
Hemodialysis duration	0.014	3.509	1.014 (0.999-1.030)	0.061
Na	-0.303	6.426	0.739 (0.584-0.934)	0.011
Total protein	-2.015	6.426	0.133 (0.028-0.633)	0.011
CRP	0.012	0.615	1.012 (0.982-1.048)	0.433
Hemoglobin	-0.256	0.656	0.774 (0.416-1.439)	0.418
HT	-0.024	0.001	0.977 (0.227-4.196)	0.975
DM	0.642	0.806	1.899 (0.468-7.707)	0.369
CAD	-0.468	0.283	0.626 (0.112-3.509)	0.595

B: beta; CAD: coronary artery disease; CI: confidence interval; CRP: C-reactive protein; DM: diabetes mellitus; HT: hypertension

with HD duration longer than 3 years at baseline. Moreover, in patients with AVF, the highest overall survival was observed in patients treated with a combination of high-flux dialyzer and ultrapure dialysate. We believe the results in this study may be associated with the possibility of more effective dialysis with higher blood flow rates in patients using AVF. Although our study had a relatively short-term follow-up, there was no positive contribution of ultrapure dialysate use on mortality in accordance with the literature.

Bacterial products in dialysate were shown to trigger inflammatory reactions (9). For patients undergoing HD, dialysate purity and dialysate content, water-sourced exogenous bacterial endotoxins, biofilm layers in dialysis storage tanks, and distribution system play a major role in systemic inflammatory responses. As a result, well-organized water systems have vital importance for HD units. Many studies have shown that the use of ultrapure dialysate reduces inflammation markers and oxidative stress, and increases serum albumin and hemoglobin levels in addition to reducing erythropoietin requirements (20, 21). It has been shown that erythropoietin requirement and resistance are reduced, as well as anemia control is facilitated because of a lower endotoxin exposure achieved by obtaining ultrapure dialysate (15, 22). In our study, anemia control was better in the ultrapure dialysate group than in the standard dialysate group, in accordance with literature. In our study, the ESA and iron doses were lower in the ultrapure dialysate group than in the standard dialysate group, as reported in literature. Annual ESA and iron doses would provide important information to compare the two groups in terms of cost.

Chronic inflammation is associated with adverse clinical outcomes such as rapid atherosclerosis and malnutrition in patients undergoing HD (20). Circulating endotoxin levels have been shown to be associated with vascular stiffness and systemic inflammation in patients undergoing HD (1). The same study found that although the use of ultrapure dialysate lowered the circulating endotoxin levels, there was no clear decrease in serum bacterial DNA levels. CRP levels continued to be elevated. It has also been shown that IL-6 levels may be a more sensitive marker than CRP for inflammation (23). In our study, in accordance with literature, the group using ultrapure dialysate did not have lower CRP levels than the group using standard dialysate. In our study, CRP levels were found to be higher in the ultrapure dialysate group, and this elevation was associated with the longer duration of HD. Moderately elevated CRP levels may be associated with conditions such as obesity, insulin resistance, subclinical inflammation, fatigue, depression, and sleep disturbance in dialysis patients. In addition, moderate CRP elevation may be due to uremia and dialysis-related factors. The dialysis procedure itself is a factor that directly initiates the inflammatory process (24, 25). Although the patients included in the study were from different centers, we believe that the dialysis center effect will be minimal on the results of the study, as the dialysis machines used in these centers are similar and the biochemical and bacteriological evaluations of the water system are in accordance with international standards. Longer total HD duration of patients in the ultrapure dialysate group may be the main factor for CRP elevation. Although the ultrapure dialysate group had higher CRP levels, lower ferritin and iron levels suggest that CRP elevation could be due to non-inflammatory and non-infectious causes.

The use of ultrapure dialysate reduces lipoprotein (a) levels and cardiovascular disease risk and mortality in patients undergoing HD (26). Over a 6-month period, the use of ultrapure dialysate reduced serum myeloperoxidase, highly sensitive CRP levels, non-HDL cholesterol, and apolipoprotein B levels. In our study, there was no difference between the two groups in terms of lipid profile, which is the classic cardiovascular risk factor.

In addition, the use of ultrapure dialysate is associated with lower β 2 microglobulin levels and the development of lower dialysis-related amyloidosis (27). The use of ultrapure dialysate was shown to have less development of intradialytic hypotension (28) and better preservation of residual renal function than the standard dialysate group (29).

With developing technologies and innovations in water systems, increasing costs come to the agenda. A study assessing the use of ultrapure water in terms of cost efficiency in the USA fully accepted ultrapure dialysate and showed potential savings of $371 to $425 million per year (30). Although clinical practice guidelines in Europe and Japan recommend the use of ultrapure dialysate, concerns about cost lead to its limited use (31, 32). However, the reduction in erythropoietin requirements after using ultrapure dialysate may counter these concerns in terms of cost (21).

Our study has some limitations. First, the study was completed with relatively few patients and in a limited region. Second, the mortality assessment in our study was limited to 1-year period.

CONCLUSION

The use of ultrapure dialysate was not identified to be superior to conventional purity dialysate use in terms of mortality and dialysis sufficiency during the 1-year follow-up. However, the use of ultrapure dialysate provided better anemia control in patients undergoing HD. In addition, the use of ultrapure dialysate may be more advantageous in terms of malnutrition.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee of Hitit University (Approval Date: January 29, 2019; Approval Number: 2019-37).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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