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Dialysis Fluid Endotoxin Level and Mortality in Maintenance Hemodialysis: A Nationwide Cohort Study

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Background: The quality of dialysis fluid water might play an important role in hemodialysis patient outcomes. Although targeted endotoxin levels of dialysis fluid vary among countries, evidence of the contribution of these levels to mortality in hemodialysis patients is lacking.

Study Design: Retrospective cohort study using data from the Japan Renal Data Registry, a nationwide annual survey.

Setting & Participants: 130,781 patients receiving thrice-weekly in-center hemodialysis for more than 6 months were enrolled at 2,746 facilities in Japan at the end of 2006. None of the patients changed facility or treatment modality during 2007.

Predictor: Highest endotoxin level in dialysis fluid reported by each facility during 2006. Patients were categorized by facility endotoxin level into the following groups: <0.001, 0.001 to <0.01, 0.01 to <0.05, 0.05 to <0.1, and ≥0.1 EU/mL. Age, sex, dialysis vintage, diabetes mellitus as a primary cause of end-stage renal disease, Kt/V, normalized protein catabolic rate, dialysis session duration, serum albumin, and hemoglobin were measured as potential confounders.

Outcome: All-cause mortality, censored by transplantation; withdrawal from dialysis treatment; or end of follow-up.

Results: Of 130,781 hemodialysis patients, 91.2% had facility endotoxin levels below the limit set for dialysis fluid in Japan (<0.05 EU/mL). During a 1-year follow-up, 8,978 (6.9%) patients died of all causes. The rate of all-cause mortality at 1 year was highest in the ≥0.1-EU/mL category (88.0 deaths/1,000 person-years). Patients in the ≥0.1-EU/mL group exhibited an increased risk of all-cause mortality of 28% (95% CI, 10%-48%) compared to the <0.001-EU/mL group.

Limitations: Endotoxin level in dialysis fluid is reported as categorical data. No information about variation in endotoxin levels in dialysis fluid over time.

Conclusions: Higher facility endotoxin levels in dialysis fluid may be related to increased risk for all-cause mortality among hemodialysis patients. Correcting this modifiable facility water management practice might improve the outcome of hemodialysis patients.

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INDEX WORDS: Hemodialysis (HD); end-stage renal disease (ESRD); mortality; dialysis fluid; ultrapure dialysate; water quality; endotoxin level; bacterial contamination; microbial contamination; dialysis facility; Japan Renal Data Registry (JRDR).

Because hemodialysis (HD) patients are exposed to a relatively large volume (350-500 L) of dialysis fluid every week, depending on session duration and flow rate, they are particularly vulnerable to contaminants in this fluid. Furthermore, the thin dialysis membrane between blood and dialysis fluid for HD patients might facilitate transfer of toxins directly into the bloodstream, adversely affecting the outcome of HD patients.

The Japanese Society for Dialysis Therapy (JSDT) therefore has advocated strict standards to ensure the cleanliness of dialysis fluid,[1] with most dialysis facilities in Japan achieving high-quality water management practices for dialysis fluid.[2]

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A number of benefits of ultrapure dialysis fluid in HD patients have been reported in case-series studies for surrogate clinical outcomes, such as prevention of carpal tunnel syndrome,[3] improvement in nutritional and inflammatory parameters,[4] increase in erythropoietin responsiveness,[5] and preservation of residual kidney function.[6] However, to our knowledge, few large cohort studies have evaluated the association between water quality and mortality in HD patients.

The relatively low mortality rate of Japanese HD patients compared with those of other countries might be due in part to the high standard of quality control for dialysis fluid. In this study, we investigated the impact of endotoxin levels in dialysis fluid, one of the most important water quality indexes, on the mortality of in-center HD patients using the Japan Renal Data Registry (JRDR) of the JSDT.

METHODS

Data Sources and Participant Selection

In this cohort study, data were obtained from the annual JRDR census, which is conducted nationwide by the JSDT. This census of dialysis patients in Japan is conducted on a voluntary basis at the end of each year. The JRDR contains data including demographics (eg, age, sex, primary cause of end-stage renal disease [ESRD], and dialysis vintage), laboratory examination findings (eg, serum creatinine, serum urea nitrogen, serum albumin, and hemoglobin values), and clinical indexes regarding dialysis treatment (eg, Kt/V, normalized protein catabolic rate [nPCR], and session duration). Detailed information of the JRDR has been described previously.[7] Using a standard analysis file (JRDR09103) obtained with permission from the JSDT (Fig 1), we analyzed 130,781 in-center HD patients who received dialysis fluid with an endotoxin level at baseline, received 3 HD sessions per week, underwent at least 6 months of treatment by the end of 2006, and did not change dialysis facilities or modalities during 2007.[8,9] A nationwide statistical survey of the JRDR for 2007 was conducted for all dialysis facilities in Japan (n = 4,098), with 4,052 (98.9%) facilities responding to the survey.[8]

Definition of Main Exposure: Endotoxin Level in Dialysis Fluid

The main exposure to be tested was facility-reported endotoxin level in dialysis fluid, which is a facility water quality indicator, reported by 2,746 facilities at the end of 2006. The highest endotoxin level in dialysis fluid during a year at each facility was reported by the manager in the annual questionnaire. Facility endotoxin levels were categorized into 5 groups on the JRDR questionnaire: <0.001 (including undetectable level) as reference, 0.001 to <0.01, 0.01 to <0.05, 0.05 to <0.1, and ≥0.1 EU/mL.

Outcome Measures

All-cause mortality during the study period was set as the main outcome measure. Mortality data were collected from the JRDR from December 31, 2006, through December 31, 2007 (follow-up, 1-12 months). Time at risk was from the start date of observation (January 1, 2007) until all-cause death, departure from the observation (as a result of transplantation or withdrawal from dialysis treatment), or end of follow-up (December 31, 2007).

Statistical Analysis

The hazard ratio (HR) of all-cause death during the study period was estimated using Cox proportional hazard regression analysis. The adjusted model was controlled for age, sex, dialysis vintage, diabetes mellitus as a primary cause of ESRD or not, Kt/V, nPCR, session duration, serum albumin level, and hemoglobin level. All models accounted for facility clustering effect. Proportional hazard assumptions of Cox regression analysis were checked graphically and with Schoenfeld residuals. An ordinal variable was created to assess the trend across the 5 different endotoxin levels in dialysis fluid. Multiple imputation using chained equations was used to estimate the models with missing covariates.[10] Complete data set analysis with list-wise deletion also was performed as a sensitivity analysis. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SAS (version 9.2; SAS Institute Inc) and Stata/SE (version 12.1; StataCorp LP) for Microsoft Windows software.

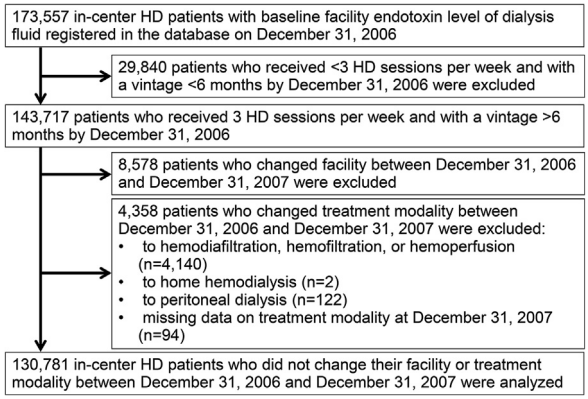

Figure 1. Selection process for analyzed patients using data from the Japan Renal Data Registry. Abbreviation: HD, hemodialysis.

RESULTS

Study Population and Demographic Characteristics of Patients

A total of 130,781 patients receiving in-center HD were analyzed. Figure 1 shows the selection process for these patients using JRDR data from 2006 through 2007. Table 1 lists patient characteristics at baseline overall and stratified by the 5 categories of facility endotoxin level in dialysis fluid.

Of 130,781 HD patients, mean age was 64.8 years, 61.3% were men, mean dialysis vintage was 7.47 years, and diabetes was diagnosed as a primary cause of ESRD in 32.4% (Table 1). Clinical index of dialysis treatment and laboratory findings also are listed in Table 1. Overall mean Kt/V was 1.37, nPCR was 0.90 g/kg/d, dialysis session duration was 234 minutes, serum albumin level was 3.78 g/dL, and hemoglobin level was 10.3 g/dL. Clinical characteristics were similar across endotoxin level groups.

Distribution of Endotoxin Levels in Dialysis Fluid

Figure 2 shows the distribution of facility endotoxin levels in dialysis fluid used to treat in-center HD patients in Japan. The JSDT sets the maximum acceptable level of endotoxins at 0.05 EU/mL in standard dialysis fluid and 0.001 EU/mL in ultrapure dialysis fluid. The proportion of Japanese HD patients