The Effect of On-line High-flux Hemofiltration Versus Low-flux Hemodialysis on Mortality in Chronic Kidney Failure: A Small Randomized Controlled Trial

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Background: Given the paucity of prospective randomized controlled trials assessing comparative performances of different dialysis techniques, we compared on-line high-flux hemofiltration (HF) with ultrapure low-flux hemodialysis (HD), assessing survival and morbidity in patients with end-stage renal disease (ESRD).

Study Design: An investigator-driven, prospective, multicenter, 3-year-follow-up, centrally randomized study with no blinding and based on the intention-to-treat principle.

Setting & Participants: Prevalent patients with ESRD (age, 16 to 80 years; vintage $>$ 6 months) receiving renal replacement therapy at 20 Italian dialysis centers.

Interventions: Patients were centrally randomly assigned to HD (n = 32) or HF (n = 32).

Outcomes & Measurements: All-cause mortality, hospitalization rate for any cause, prevalence of dialysis hypotension, standard biochemical indexes, and nutritional status. Analyses were performed using the multivariate analysis of variance and Cox proportional hazard method.

Results: There was significant improvement in survival with HF compared with HD (78%, HF versus 57%, HD) at 3 years of follow-up after allowing for the effects of age ($P = 0.05$). End-of-treatment Kt/V was significantly higher with HD (1.42 $\pm$ 0.06 versus 1.07 $\pm$ 0.06 with HF), whereas β_2-microglobulin levels remained constant in HD patients (33.90 $\pm$ 2.94 mg/dL at baseline and 36.90 $\pm$ 5.06 mg/dL at 3 years), but decreased significantly in HF patients (30.02 $\pm$ 3.54 mg/dL at baseline versus 23.9 $\pm$ 1.77 mg/dL; $P < 0.05$). The number of hospitalization events for each patient was not significantly different (2.36 $\pm$ 0.41 versus 1.94 $\pm$ 0.33 events), whereas length of stay proved to be significantly shorter in HF patients compared with HD patients ($P < 0.001$). End-of-treatment body mass index decreased in HD patients, but increased in HF patients. Throughout the study period, the difference in trends of intradialytic acute hypotension was statistically significant, with a clear decrease in HF ($P = 0.03$).

Limitations: This is a small preliminary intervention study with a high dropout rate and problematic generalizability.

Conclusion: On-line HF may improve survival independent of Kt/V in patients with ESRD, with a significant decrease in plasma β_2-microglobulin levels and increased body mass index. A larger study is required to confirm these results.

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INDEX WORDS: Hemodialysis; hemofiltration; high flux; dialysis adequacy.

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Advances in renal replacement therapy have significantly improved survival in patients with end-stage renal disease (ESRD) during the past few decades, although life expectancy remains suboptimal compared with the general population.[1-3]

High β_2-microglobulin removal[4] and high-flux treatments[5] have been associated with significant improvements in the survival of patients with ESRD, but a causal association has never been confirmed in the few randomized studies

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available. The Hemodialysis (HEMO) Study,[6] the largest clinical trial comparing high and low flux and comparing high and low dose in a 2 × 2 factorial design found no significant improvements in survival and morbidity with high-flux membranes. However, in the HEMO Study, the amount of convection (maximum, 30 to 40 mL/min in the high-flux modality, mostly stemming from internal filtration) was significantly less than what could be obtained with typical convective treatments.[7] Moreover, in randomized studies comparing convective and diffusive techniques,[8,9] hemodialysis (HD) has always been exclusively or prevalently compared with hemodiafiltration (HDF). In the latter, convection is complementary to diffusion, and the greater convective quota compared with HD is never maximized, to the extent that it reaches 20 L/session at most. The case of hemofiltration (HF) is different. This technique operates exclusively by convection and mimics the activities of the kidney more closely.[10] High fluxes and removal of large-sized molecules may be obtained in HF with the new on-line techniques and only by a convective process. In this setting, we performed the first-ever randomized, prospective, multicenter, controlled, clinical trial designed to evaluate the comparative long-term effects of a pure convective therapy, on-line predilution HF, versus ultrapure HD, assessing mortality and morbidity outcomes in patients with ESRD.

METHODS

This was an investigator-driven, prospective, multicenter, 3-year follow-up, centrally randomized study with no blinding and based on the intention-to-treat principle. The study was designed to compare the long-term effects of a pure convective therapy, on-line predilution HF, versus ultrapure bicarbonate HD with biocompatible membranes on mortality and morbidity outcomes in patients with ESRD. Patients were enrolled in the study on the basis of the following inclusion and exclusion criteria.

Inclusion Criteria

Inclusion criteria were age of 16 to 80 years, dialysis treatment for at least 6 months with conventional HD, residual kidney function less than 2 mL/min/1.73 m^2 (calculated as the mean of urea and creatinine clearance with 24-hour urine collection; glomerular filtration rate in mL/min/1.73 m^2 may be converted to mL/s/1.73 m^2 by multiplying by 0.01667), Charlson Comorbidity Index of 3 or higher; and presence of cardiovascular instability during dialysis in at least 15% of sessions.

Exclusion Criteria

Exclusion criteria were neoplasia (any), acute clinical conditions (myocardial infarction, congestive heart failure, stroke, recent surgery, or severe sepsis) within 3 months of enrollment in the study, any vascular access dysfunction (patients with central catheters were admitted if blood flow rate was ≥300 mL/min), residual urinary output greater than 200 mL/24 h, and body weight greater than 75 kg.

Interventions and Comparison

Predilution on-line HF was the experimental intervention and was compared with ultrapure HD. Both dialysis modalities were performed using the same dialysis machine (Gambro AK 100 Ultra; Gambro, Lund, Sweden). To account for possible confounding by membrane and fluid type, the same membrane materials (polyamide) and ultrapure fluids (dialysate in HD, infusate in HF) at the same temperature (37°C) were used. Poliflux 8L (polyamide, 1.7 m^2; ultrafiltration coefficient, 12.5 mL/min/mm Hg; Gambro) and Poliflux 21S (2.1 m^2; ultrafiltration coefficient, 83 mL/min/mm Hg; Gambro) dialyzers were used during HD and HF, respectively. In HD, ultrapure dialysate at 500 mL/min, 37°C, was prepared by the machine by 2 U-800S polyamide Gambro ultrafilters. In HF, a sterile nonpyrogenic substitution solution, 37°C, sterilized with 2 U-8000S and 1 disposable U-2000 filter, was infused in blood at the prefilter. Target infusate volume was aimed at 120% of dry body weight, which is why we excluded from enrollment patients with a body weight greater than 75 kg, who would have required a huge amount of infusion fluid.

The composition of dialysate and infusate was the same: sodium, 140 mEq/L; potassium, 2 mEq/L; calcium, 1.5 mEq/L; glucose, 100.9 mg/dL (glucose in mg/dL may be converted to mmol/L by multiplying by 0.05551); and bicarbonate, 30 mEq/L.

Outcomes

All-cause mortality and overall morbidity were assessed during a 3-year follow-up period based on the intention-to-treat principle. In addition to all-cause mortality, the following variables were measured: hospitalization rate, defined as number of hospitalization events per patient and length of stay per single event; prevalence of dialysis sessions with at least 1 episode of acute hypotension; all standard biochemical parameters; and some indicators of nutritional status.

Hypotension was defined as: (1) any symptomatic decrease in systolic arterial pressure by 20 mm Hg or more compared with the predialysis value requiring nursing intervention (any fluid administration or transient withdrawal of ultrafiltration); (2) for patients with predialysis systolic arterial pressure greater than 100 mm Hg, a systolic arterial pressure of 90 mm Hg or less, even in the absence of typical symptoms of decreased blood pressure; and (3) for patients with predialysis systolic arterial pressure less than 100 mm Hg, systolic arterial pressure decrease by at least 10% of the predialysis value, accompanied by characteristic symptoms (nausea, vomiting, sweating, dizziness, and yawning).

Blood chemistry was tested in both arms at baseline and every 4 months on a midweek day, with pretreatment and posttreatment determinations of the following variables: