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Original Investigation

# A Randomized, Single-Blind, Crossover Trial of Recovery Time in High-Flux Hemodialysis and Hemodiafiltration

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**Background:** The choice between hemodiafiltration (HDF) or high-flux hemodialysis (HD) to treat end-stage kidney disease remains a matter of debate. The duration of recovery time after treatment has been associated with mortality, affects quality of life, and may therefore be important in informing patient choice. We aimed to establish whether recovery time is influenced by treatment with HDF or HD.

**Study Design:** Randomized patient-blinded crossover trial.

**Settings & Participants:** 100 patients with end-stage kidney disease were enrolled from 2 satellite dialysis units in Glasgow, United Kingdom.

**Intervention:** 8 weeks of HD followed by 8 weeks of online postdilution HDF or vice versa.

**Outcomes:** Posttreatment recovery time, symptomatic hypotension events, dialysis circuit clotting events, and biochemical parameters.

**Measurements:** Patient-reported recovery time in minutes, incidence of adverse events during treatments, hematology and biochemistry results, quality-of-life questionnaire.

**Results:** There was no overall difference in recovery time between treatments (medians for HDF vs HD of 47.5 [IQR, 0-240] vs 30 [IQR, 0-210] minutes, respectively; $P = 0.9$). During HDF treatment, there were significant increases in rates of symptomatic hypotension (8.0% in HDF vs 5.3% in HD; relative risk [RR], 1.52; 95% CI, 1.2-1.9; $P < 0.001$) and intradialytic tendency to clotting (1.8% in HDF vs 0.7% in HD; RR, 2.7; 95% CI, 1.5-5.0; $P = 0.002$). Serum albumin level was significantly lower during HDF (3.2 vs 3.3 g/dL; $P < 0.001$). Health-related quality-of-life scores were equivalent.

**Limitations:** Single center; mean achieved HDF convection volume, 20.6 L.

**Conclusions:** Patients blinded to whether they were receiving HD or HDF in a randomized controlled crossover study reported similar posttreatment recovery times and health-related quality-of-life scores.



***INDEX WORDS:*** Hemodialysis (HD); high-flux HD; hemodiafiltration (HDF); recovery time; intradialytic hypotension; symptomatic hypotension; blood pressure; dialysis circuit clotting; dialysis modality; end-stage kidney disease (ESKD); quality of life; randomized controlled trial (RCT).

End-stage kidney disease has a significant and deleterious impact on duration and quality of life.[1-4] Approximately 1.9 million patients receive renal replacement therapy worldwide.[5] Intermittent renal replacement therapy remains essential for many, and extracorporeal treatments for end-stage kidney disease such as hemodialysis (HD) and hemodiafiltration (HDF) have a higher incidence and prevalence than peritoneal dialysis, particularly in the developed world.[6-8]

Observational data have suggested that HDF is beneficial. However, randomized controlled trial (RCT) data comparing HDF with HD have produced mixed results, with analyses (mainly post hoc) suggesting that HDF has superior cardiovascular and mortality outcomes limited to patients receiving the highest convection volumes.[9-14] Although this is encouraging, high convection volumes may not be achievable in HDF patients who have suboptimal vascular access and/or time constraints associated with real-life dialysis provision.[15]

Factors influencing patient preference and choice are becoming more prominent. Patients treated with HD have lower health-related quality-of-life (HRQoL)

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scores than the general population, and this is associated with increased morbidity and mortality.[16,17] Although some previous studies have shown an improvement in HRQoL with convective treatments compared to HD,[3,4] the largest RCT to have studied this outcome found no difference between HDF and low-flux HD.[9] Length of recovery time after dialysis is an important patient-reported outcome measure that adversely affects HRQoL, and evidence from the Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort has suggested an association between longer postdialysis recovery time and increased mortality.[18]

We performed a patient-blinded randomized crossover study of patient-reported recovery time to determine whether recovery time differs between HD and HDF.

## METHODS

### Study Design

A patient-blinded, randomized, controlled, crossover design was used. Patients were randomly assigned in a 1:1 ratio to receive 8 weeks of HD followed immediately by 8 weeks of online post-dilution HDF, or vice versa. Patients were recruited from 2 satellite dialysis units (Stobhill Hospital and Glasgow Royal Infirmary) and consented by E.B., N.Z., J.R.S., or R.M. The study ran from July 2013 through March 2014. Randomization was conducted by E.B. using a remote telephone-based system run by the Robertson Centre for Biostatistics, University of Glasgow, United Kingdom.

The study was conducted in accordance with the ethics principles of the Declaration of Helsinki; all patients provided written informed consent. Good Clinical Practice guidelines were followed throughout. The West of Scotland Research and Ethics Committee approved the study (13/WS/0010). Anonymized data were sent to the Robertson Centre for Biostatistics for analysis. Data analysis programs were developed prior to the release of randomization codes to the study statistician.

### Patient Selection

There were 198 patients screened for eligibility. Inclusion criteria were receiving HD for more than 90 days, reliable vascular access, and age of 18 years or older. Exclusion criteria were currently receiving HDF (however, no recruited patients ended up having previous HDF exposure), life expectancy less than 6 months, active neoplasia, recent (within 1 month) emergency hospital admission, and unable to give informed consent or complete questionnaires. Of 119 patients meeting these criteria, 100 underwent randomization, stratified by age (4 strata: 18-49, 50-59, 60-69, and ≥70 years) and sex (given sex differences noted in recovery time reporting[18]) into one of 2 groups: HD followed by HDF, or HDF followed by HD. A separate randomization list was generated for each stratum by a computer program, using the method of randomized permuted blocks of length 4.

### Treatments

Patients received 3 treatment sessions per week. Dialysis time, dialyzer blood flow rate, dialysate flow rate, postdialysis weight, and medications were kept constant unless changes were required on clinical grounds. High-flux dialyzers (FX80 or FX100; Fresenius) were used to remain consistent with patients' previous dialyzers and reduce the risk for inadvertent unblinding. Dialysate composition was as follows: sodium, 138 mmol/L; potassium, 2 mmol/L; chloride, 108.5 mmol/L; bicarbonate, 32 mmol/L; acetate, 3 mmol/L; calcium, 1.25 mmol/L; magnesium, 0.5 mmol/L; and glucose, 1 g/L. Fresenius 5008 dialysis machines were used. To further ensure patient blinding, dialysis machines were turned away and the on-screen treatment modality notification was covered. Dialysis unit staff were not blinded to treatment allocation.

### Outcomes

The primary outcome was reported recovery time in minutes. On arrival for each session, patients were asked by the treating nurse to state how long it took them to recover completely from the preceding session. Secondary outcomes were frequency of symptomatic hypotension; frequency of intradialytic clotting events; pre–dialysis session serum concentrations of potassium, phosphate, vitamin $B_{12}$, parathyroid hormone, $\beta_2$-microglobulin, betaine, and interleukin 6; and Kt/V of urea.

### Measurement Methods

Predialysis hematologic and biochemical tests were performed following a 1-day treatment gap. Blood results from the middle and end point of each treatment period were used in the analysis. The nurses administering treatments were responsible for documenting primary and secondary end point data, as well as routine dialysis session duties and data collection.

Although not prespecified outcomes, the frequency of other adverse events (documented in free-text format by nursing staff), change in quality-of-life scores (Kidney Disease Quality of Life–Short Form [KDQOL-SF], version 1.3[19]), change in dialysis dose, and patients' preferred dialysis modality at the end of the study were also recorded. This was overseen by a dedicated research nurse, who also administered the KDQOL-SF, version 1.3, questionnaires and processed blood samples.

### Sample Size Calculation

This was based on pilot data demonstrating the variation in recovery times in 100 patients over 3 consecutive HD sessions. To detect a 20% absolute reduction in recovery time with 90% power, we calculated that 82 patients would need to complete the study (41 in each group). We planned to randomly assign 100 patients in total, allowing for a dropout rate of 18%.

### Statistical Analyses

Analyses were performed on an intention-to-treat basis. Baseline characteristics and Charlson comorbidity scores[20] were compared between groups (HD then HDF vs HDF then HD) by Fisher exact tests for categorical variables and *t* tests for continuous variables (or Wilcoxon tests if needed). Given that the distribution of recovery times was bimodal with a peak at zero, recovery times were analyzed by crossover analysis with 2 mixed models. A generalized linear mixed model (logistic regression with random effect) was run to model the odds for a patient to recover immediately (recovery time = 0 minutes) and a mixed model was run to model the delayed (recovery time > 0 minutes) recovery times (after a logarithmic transformation). The models were combined by Monte Carlo simulations, then a parametric bootstrap method was used to obtain the overall *P* value.[21] Correlation between recovery times across successive sessions were modeled with an autoregressive model of order 1 (in which each recovery time is dependent on the previous session, and so on) by treatment and time period. Additional analyses were run for blood tests, dialysis data, Kt/V, and mean blood flow. Hypotension, clotting, and adverse events were compared between the treatments by relative risk (RR), and in order to take into account the crossover design, odds ratios (ORs) obtained by logistic regression (with random effects) were also calculated. The KDQOL survey was compared between treatments and baseline with Friedman tests.