# Higher convection volume exchange with on-line haemodiafiltration is associated with survival advantage for dialysis patients: the effect of adjustment for body size

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Abstract

Mortality remains high for hemodialysis (HD) patients. On-line hemodiafiltration (Ol-HDF) removes more middle sized uremic toxins. However, outcomes of individual trials comparing Ol-HDF with HD have been discrepant while secondary analyses reported higher convective volumes improved survival. Higher convection volumes are easier to achieve in larger patients. We examined different methods to standardise Ol-HDF convection volume on all-cause and cardiovascular mortality compared to HD. Pooled individual patient analysis of four prospective trials compared thirds of delivered convection volume with HD. Convection volumes were either not standardised, or standardised to weight, body mass index (BMI), body surface area (BSA) and total body water (TBW). Multivariable Cox proportional hazards models were used to obtain hazard ratios and 95% confidence intervals. We analysed data from 2793 patients and all-cause mortality was reduced when convective dose was unstandardised or standardised to BSA and TBW; HR 0.65 (0.51-0.82), 0.74 (0.58 -0.93 ), and 0.71 (0.56 -0.93) for those receiving higher convective doses. Standardisation by body weight or BMI gave no significant survival advantage. Higher convection volumes are generally associated with greater survival benefit with OL-HDF, but results vary across different ways of standardisation for body size. Further studies should take body size into account when evaluating the impact of delivered convection volume on mortality endpoints.

## Introduction

The mortality for haemodialysis patients remains high, with survival probability in the UK at one, three and five years being around 90, 70 and 50%, respectively [1]. Intuitively a greater amount of dialysis by removing more azotaemic toxins or achieving a critical threshold would be expected to increase patient survival. The National Co-operative Dialysis Study (NCDS), reported that lower time averaged urea concentrations improved short term patient outcomes, and defined a critical sessional urea clearance threshold for haemodialysis adequacy [2]. However later studies failed to demonstrate any survival benefit with greater urea clearance (HEMO study) [3],

Solute clearance during dialysis is predominantly by diffusion. Adding a convective clearance increases middle sized molecule removal. During high flux haemodialysis treatments there is some convective transport due to back filtration [4], so increasing middle molecule clearances [5]. However with online post dilution haemodiafiltration much higher volume exchanges can be achieved [6]. There have been a recent series of publications of trials comparing online haemodiafiltration with standard haemodialysis treatments. Only one of the three trials, reported a survival benefit [7], and this trial differed by delivering the highest convection volume. Individual patient analysis of the three trials [8,9], confirmed a survival advantage for high volume convection exchange [10].

Although the CONTRAST study was designed to provide high volume online haemodiafiltration treatments [8], there was a wide variation in the delivered convective volumes particularly between centres [11]. It is well recognised that blood flow and sessional time are important in determining convective exchange [12], but we wished to determine whether there were additional patient or treatment related factors were important in achieving higher volume convective exchanges.

## Methods and Patients

We audited the convective volume recorded in 653 adult outpatient dialysis patients attending for thrice weekly treatments from a single mid-week session. Online haemodiafiltration using Fresenius F4000H, 5000H dialysis machines (Fresenius Bad Homburg, Germany), or Braun Dialog+® (BBraun, Melsungen, Germany) dialysis machines with integrated blood pressure monitoring, polysulfone high flux dialyzers (Nipro Corporation, Osaka, Japan) [13], with ultrapure quality dialysis water at a modal temperature of 35°C and anticoagulated with bolus of low molecular weight heparin into the venous blood line (tinzaparin, Leo Laboratories, Princes Risborough, UK) [14]. Delivered dialysate sodium was regularly checked by both flame photometry and ion electrophoresis methods [15].

Central venous access catheter access was with dual lumen Ash split catheters (Kimal plc, Uxbridge, UK).

Pre and post-dialysis dialysis blood samples were measured using a standard laboratory auto-analyser (Roche Integra, Roche diagnostics, Lewes, UK), with an indirect ion selective electrode technique for sodium, and pre-dialysis serum sodium was also corrected for glucose interference [16]. Serum albumin was determined by the bromcresol green method and haemoglobin by auto-analyser (XE-2100 Sysmex Corporation, Kobe, Japan) [17].

Blood pressure was taken in a standardized manner both immediately prior to starting dialysis and post-dialysis in the non-fistula arm whilst in the sitting position using the haemodialysis machine integrated electronic blood pressure monitor. In cases of dialysis machines without functioning integral blood pressure measuring devices then blood pressure was measured using a Dinamap® (Dinamap Pro100, Critikon, Tampa, USA). Patients did not receive intravenous iron, or erythropoietin stimulating agents during their midweek dialysis session.

Total body water (TBW), extracellular water (ECW) and intracellular water (ICW) were measured using multi-frequency bioelectrical impedance analysis (MFBIA) pre and then approximately 20 minutes post the mid-week dialysis session (InBody 720 Body Composition Analysis, Biospace, Seoul, South Korea) [18]. Height and weight were measured using calibrated scales [19], and body mass index (BMI) and body surface area (BSA) derived by standard methods [10,20]. The Stoke-Davies co-morbidity scoring system was used to grade co-morbidity [21].

Ethical approval for this retrospective audit fulfilled the UK National Health Service audit and clinical service development guidelines.

## Statistical analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, or percentage. Statistical analysis was by Chi square analysis, corrected for small numbers by Yates' correction, Comparison was made by anova or Kruskal Wallis, with post hoc testing by Tukey or Dunn's methods. Univariate correlation was with Pearson or Spearman's test, and then if variables with a $p<0.1$ value were then analysed in a multivariable step backward regression analysis, with appropriate conversion of non-parametric data by log transformation, and then excluding variables that were not statistically relevant unless they improved model fit. Statistical analysis used Graph Pad Prism version 6.0 (Graph Pad, San Diego, CA, USA), and SPSS version 21 (University Chicago, USA), and statistical significance was taken at or below the 5% level.

## Results

We reviewed the records of 653 adult patients, mean patient age was 64.9±14.9 years, 65.3% male, and 47.7% of patients had diabetes. The commonest ethnic group was Caucasoid (39.8%), followed by South Asian (27%), African-Afro-Caribbean (25.3%) and Far Asian (5.8%). 533 patients dialysed using arterio-venous fistula (AVF) access, 69 central venous access catheters (CVC) and 51 arterio-venous grafts (AVG). 18.2% were Davies co-morbidity grade 0, 59.6% grade 1 and 22.2% grade 2. Weight pre-dialysis was 72.2±15.9, post dialysis 70.415.8 kg, TBW predialysis 37.2±9.1 L, postdialysis 35.3±8.4, ratio ECW/TBW predialysis 0.402±0.025 and post-dialysis 0.392±.0.021. Systolic blood pressure pre-dialysis was 142.2±26.8, and post-dialysis 129.6±24.2 mmHg, with corresponding diastolic blood pressures of 74.4±15.6 and 69.6±15.1 mmHg, respectively.

Dialysis parameters are described in Table 1 along with pre-dialysis blood test results. Urea reduction ratio was 75.4±5.9%, and single pool KtVurea 1.46±0.23.

Discussion

Our

Funding

The authors have the following conflicts of interest:

Andrew Davenport no conflicts of interest

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Table 1: Patient demographics comparing haemodialysis (HD) and On-line haemodiafiltration (Ol-HDF). Pre-dialysis haemoglobin and biochemical variables. Results expressed as number, percentage (%), or mean (standard deviation) or median (interquartile range). History of cardiovascular disease (CVD), diabetes mellitus (Diabetes).

| Dialysis variable | |
|---|---|
| Session time hours | 3.80 ±0.46 |
| Convection volume L | 17.0±3.5 |
| Convection volume ml/min | 74.4±13.5 |
| Blood flow ml/min | 321.4±26.3 |
| Dialysate flow ml/min | 500 (500-550) |
| Dialyzer surface area $m^2$ | 1.89±0.2 |
| Dialysate temperature $^0C$ | 35.0 (35.0-35.5) |
| Dialysate sodium mmol/L | 137.0±1.3 |
| Dialysate potassium mmol/L | 2.0 (1.0-2.0) |
| Dialysate calcium mmol/L | 1.35 (1.0-1.35) |
| Dialysate bicarbonate mmol/L | 32.0 (32.0-32.0) |
| Dialysate acetate mmol/L | 3.0 (3.0-3.0) |
| Haematocrit % | 0.349±-0.041 |
| Serum sodium mmol/L | 138.9±3.5 |
| Serum albumin g/L | 39.7±3.7 |
| Serum glucose mmol/L | 7.3 ±2.7 |
| C reactive protein g/L | 5 (2-11) |
| NT probrain natriuretic hormone pmol/L | 377 (140-1214) |
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Figure 1: Hazard ratios (boxes) and 95% confidence intervals (bars) for all-cause mortality in patients receiving online haemodiafiltration versus haemodialysis by convection volume, using different methods to standardise convection volume

Figure 2: Hazard ratios (boxes) and 95% confidence intervals (bars) for cardiovascular mortality in patients receiving online haemodiafiltration versus haemodialysis by convection volume, using different methods to standardise convection volume

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supplementary Figure E1: Flow chart showing recruitment of patients into the French haemodiafiltration study.