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Original Investigation

Effect of Hemodiafiltration or Hemofiltration Compared With Hemodialysis on Mortality and Cardiovascular Disease in Chronic Kidney Failure: A Systematic Review and Meta-analysis of Randomized Trials

Amanda Y. Wang, MBBS, FRACP,[1] Toshiharu Ninomiya, MD, PhD,[1] Anas Al-Kahwa, BSc(Med),[1,2] Vlado Perkovic, MBBS, PhD, FRACP,[1] Martin P. Gallagher, MBBS, PhD, FRACP,[1,2] Carmel Hawley, MBBS (Hons), M Med Sci, FRACP,[3] and Meg J. Jardine, MBBS, PhD, FRACP[1,2]

Background: Whether convective modalities of dialysis, including hemofiltration (HF) and hemodiafiltration (HDF), improve cardiovascular outcomes and mortality is unclear.

Study Design: Systematic review and meta-analysis.

Setting & Population: Patients receiving HDF, HF, or standard hemodialysis (HD).

Selection Criteria for Studies: Randomized controlled trials.

Intervention: Convective modalities of dialysis (HDF and HF) versus standard HD.

Outcomes: The primary outcome was clinical cardiovascular outcomes. Secondary outcomes were all-cause mortality, episodes of symptomatic hypotension, dialysis adequacy, and β_2-microglobulin level. Relative risks (RRs) or weighted mean differences with 95% CIs for individual trials were pooled using random-effects models.

Results: The search yielded 16 trials including 3,220 patients. Therapies assessed were convective modalities (HDF or HF) compared with standard HD. Compared with HD, convective modalities did not significantly reduce the risk of cardiovascular events (RR, 0.85; 95% CI, 0.66-1.10) or all-cause mortality (RR, 0.83; 95% CI, 0.65-1.05). Convective modalities reduced symptomatic hypotension (RR, 0.49; 95% CI, 0.30-0.81) and improved serum β_2-microglobulin levels (-5.95 mg/L; 95% CI, -10.27 to -1.64), but had no impact on small-molecule clearance (weighted mean difference in Kt/V, 0.04; 95% CI, -0.04 to 0.12). There was a nonsignificant trend to a greater likelihood of receiving a kidney transplant for participants allocated to filtration therapies (RR, 1.19; 95% CI, 0.99-1.42).

Limitations: The trials were predominantly of suboptimal quality and underpowered, with imbalance in some prognostic variables at baseline. Intention-to-treat analysis was not used in some trials. Our analysis was limited to published outcomes.

Conclusions: The potential benefits of convective modalities over standard HD for cardiovascular outcomes and mortality remain unproved. Further high-quality randomized trials are needed to define the impact of these modalities on clinically important outcomes.

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INDEX WORDS: Hemodiafiltration; hemofiltration; hemodialysis; end-stage renal disease, systematic review; meta-analysis; randomized controlled trial; clinical trial; cardiovascular diseases; all-cause mortality.

Mortality and morbidity rates for people with end-stage kidney disease are high,[1] due in part to a 15- to 30-fold increase in cardiovascular events.[2] The causes for these material increases in cardiovascular morbidity and mortality are unclear, as is the impact on them of different dialysis modalities. Increased levels of both small[3] and middle molecules are associated with increased mortality.[4-8] The linear association of declining estimated glomerular filtration rate with events, which has been described best for cardiovascular disease events,[3] has led to the hypothesis that increasing dialysis clearances, including clearances of middle molecules, may improve outcomes.

Standard hemodialysis (HD)[9] uses diffusion, the removal of solutes and water across a semipermeable membrane down a concentration gradient.[10] The convection modality hemofiltration (HF) uses increased transmembrane pressure to enhance clearance through solvent drag,[11] whereas hemodiafiltration (HDF) combines both HD and HF. Observational studies have suggested that convective modalities are associated with better removal of both small[12] and middle molecules, such as β_2-microglobulin,[5,13,14] as well as greater

From the [1]Renal and Metabolic Division, The George Institute for Global Health, Camperdown; [2]Department of Nephrology, Concord Repatriation General Hospital, Concord; and [3]Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia.

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Address correspondence to Meg J. Jardine, PhD, FRACP, Renal and Metabolic Division, The George Institute for Global Health, Camperdown, Australia. E-mail: mjardine@georgeinstitute.org.au

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hemodynamic stability,[5] improved survival,[15] and better quality of life,[16] than standard HD.

This systematic review aims to assess the current evidence from randomized trials of the impact of convective compared with standard therapies on cardiovascular, survival, and other outcomes for people receiving maintenance dialysis therapy.

METHODS

Data Sources and Searches

We performed a systematic review of the literature according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[17] for the conduct of meta-analyses of intervention trials. Electronic searches were performed using the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1946 to February 2013), and EMBASE (1980 to February 2013). Unpublished trials were sought in references of all selected studies, relevant conference proceedings, and from the ClinicalTrials.gov website. No language or date restrictions were imposed. The search included relevant text words and Medical Subject Headings, including all spellings of h(a)emodialysis, h(a)emofiltration, and h(a)emodiafiltration (Fig S1, available as online supplementary material).

Study Outcomes

The prespecified primary outcome was clinical cardiovascular outcomes, which was defined when possible as a composite of cardiovascular mortality, myocardial infarction, and stroke or otherwise as defined by study author. Secondary outcomes were all-cause mortality, episodes of symptomatic intradialytic hypotension (as defined by study author), postdialysis systolic blood pressure, neuropathy progression, quality-of-life measurements (assessed by 36-Item Short Form Health Survey [SF-36], or as defined by study author), small-molecule clearance (assessed by Kt/V), and serum β_2-microglobulin measurements.

After the trials were identified, it became clear that a number of them reported on transplantation during the study period, a clinically important event. Accordingly, we elected to perform a post hoc analysis of the likelihood of transplantation.

Study Selection

We included all randomized controlled trials (RCTs) and quasi-RCTs comparing either HDF or HF with standard HD in adults with end-stage kidney disease treated with dialysis. The first period only of randomized crossover studies was included given the possibility of a carry-over effect from the intervention on the primary outcome.[18] Acetate-free biofiltration was treated as an HF modality. Trials that did not use HD as the comparator were excluded. Two reviewers independently screened abstracts, with disputes resolved in consultation with a third investigator.

Data Extraction and Quality Assessment

Two reviewers independently extracted data using a standardized approach and prespecified protocol (available from M.J.J.). Data for participant characteristics, modality of extracorporeal renal replacement therapy, trial characteristics, and outcomes were extracted. Original investigators were contacted in an attempt to obtain missing data. Methodological quality assessment was performed using the Cochrane quality criteria (concealment of treatment allocation; blinding of outcome assessors, care providers, and participants; completeness of study and follow-up; and selective outcome reporting[18]) and application of intention-to-treat (ITT) analysis principles. Studies were defined as low risk of bias with reference to ITT analysis if they, as a minimum, analyzed nonadherent participants according to allocated randomization outcome. Studies were defined as being at low risk for selective outcome reporting if they reported at least one important clinical event (clinical cardiovascular outcomes, cardiovascular mortality, or all-cause mortality) plus a marker of dialysis clearance (small and/or middle molecule).

Data Synthesis and Analysis

Summary estimates of relative risks (RRs) were derived from a random-effects model using the Hartung and Knapp[19] method. In studies with more than one filtration or HD arm, groups were combined into a single filtration or control group. Event counts were used when available to calculate RRs with 95% confidence intervals (CIs) for dichotomous outcomes. When either or both treatment arms of a study contained no events, the value of 0.5 was added to each cell of the 2×2 table for the study. Weighted mean differences (WMDs) and 95% CIs were calculated for continuous outcomes. Hypotensive events were defined as number of treatment sessions during which the event occurred or number of patients experiencing one or more episode of these complications. The percentage of variability across all studies attributable to heterogeneity beyond chance was estimated using the I^2 index.

Prespecified subgroup analyses were conducted for the primary and major secondary outcomes of clinical cardiovascular outcomes and all-cause mortality using random-effects metaregression analyses in accordance with Cochrane guidelines[18] using the Stata metareg (StataCorp LP) command. Prespecified subgroups were: (1) convective modality type (HDF or HF) in the intervention arm and (2) flux type (high or low) in the comparator arm. Sensitivity studies were performed according to Cochrane methodology.[18] Post hoc subgroup analyses were performed according to trial quality when some variability in risk of bias was present among studies (arbitrarily defined as no more than two-thirds of the trials falling into a single risk category) and according to likelihood of kidney transplantation. The ITT analysis method for major clinical end points was characterized as: (1) inclusion of participants not adherent to randomization (ITT analysis), (2) exclusion of participants not adherent to randomization (per-protocol analysis), and (3) inclusion of participants according to treatment delivered (as-treated analysis). We accepted the proposition that transplantation reasonably could be expected to have at least an equal impact on outcomes as dialysis modality. We therefore adopted a liberal interpretation and defined studies as using ITT principles if patients were excluded only after death or transplantation.

Statistical analyses were performed with Stata, version 11.0. $P < 0.05$ was considered statistically significant for all analyses.

RESULTS

Study Selection and Characteristics

The search yielded 3,184 potentially relevant studies, of which 96 were reviewed in full text (Fig 1). Sixteen RCTs were identified, reporting on 3,220 participants (Table 1).[13,15,20-33] Interventions studied in these RCTs included HDF (11 trials; 2,916 participants), HF (4 trials; 158 participants), and either filtration modality (1 trial; 146 participants). The comparator treatment was HD using low-flux (9 trials), high-flux (5 trials), or any type (2 trials) of dialysis membrane. One trial[20] randomly assigned participants to 1 of 3 HD groups that differed according to membrane (treated as a single control group in the present analyses) or HDF. Similarly, another trial randomly assigned participants to 2 filtration groups (HDF or