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Original Investigation

Bioimpedance-Guided Fluid Management in Maintenance Hemodialysis: A Pilot Randomized Controlled Trial

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Background: Chronic subclinical volume overload happens very frequently in hemodialysis patients and is associated directly with hypertension, increased arterial stiffness, left ventricular hypertrophy, and ultimately higher mortality.

Study Design: Randomized controlled parallel-group trial.

Setting & Participants: 131 patients from one hemodialysis center, randomly assigned into 2 groups.

Intervention: Dry weight prescription using results derived from repeated 3-month bioimpedance measurements to guide ultrafiltration for strict volume control (bioimpedance group; n = 62) compared with clinical judgment without bioimpedance measures (clinical-methods group; n = 69) for 2.5 years.

Outcomes: The primary outcome was all-cause mortality over 2.5 years (the duration of the intervention). Secondary outcomes were change in relative arterial stiffness, fluid overload, and blood pressure (BP) over 2.5 years.

Measurements: Bioimpedance measurements were performed using a Body Composition Monitor device. Pulse wave velocity analysis was performed at baseline, 2.5 years (end of intervention), and 3.5 years (end of study). Relative fluid overload and BP were assessed at 3-month intervals.

Results: The unadjusted HR for all-cause death in the bioimpedance group (vs the clinical-methods group) was 0.100 (95% CI, 0.013-0.805; $P = 0.03$). After 2.5 years, we found a greater decline in arterial stiffness, relative fluid overload, and systolic BP in the bioimpedance group than the clinical-methods group. Between-group differences in change from baseline to the end of intervention were −2.78 (95% CI, −3.75 to 1.80) m/s for pulse wave velocity ($P < 0.001$), −2.99% (95% CI, −5.00% to −0.89%) for relative fluid overload ($P = 0.05$), and −2.43 (95% CI, −7.70 to 2.84) mm Hg for systolic BP ($P = 0.4$).

Limitations: Echocardiography was not performed as cardiovascular assessment and the caregivers were not masked to the intervention.

Conclusions: Our study showed improvement in both surrogate and hard end points after strict volume control using bioimpedance to guide dry weight adjustment. These findings need to be confirmed in a larger trial.

INDEX WORDS: Bioimpedance; hemodialysis; pulse wave velocity; survival.

Patients with end-stage renal disease treated with maintenance dialysis have alarmingly high mortality, similar to that seen with aggressive forms of cancer.[1] Chronic subclinical volume overload occurs very frequently and may be ubiquitous in hemodialysis (HD) patients receiving the standard thrice-weekly treatment. It is associated directly with hypertension, increased arterial stiffness, left ventricular hypertrophy, heart failure, and eventually, higher mortality and morbidity.[2]

To routinely determine patients' hydration status, clinical surrogate parameters, such as ultrafiltration rate or blood pressure (BP), are used. Unfortunately, clinical parameters often are unreliable and not always conclusive. Currently, we are not even certain of the optimal BP target for HD patients.[3] The classic empirical approach of gradually "drying out" the patient until the symptomatic hypotension ceiling is reached is difficult in one-third of patients (particularly for those with low cardiac reserve/cardiac failure) or even deleterious, leading to cardiac stunning[4] and sustained increases in brain natriuretic peptide (BNP; infraclinic myocardial damage) levels. Theoretically, these problems could be solved with a valid method for assessment of individual volemia and detection of changes in fluid volume/fluid compartments.

A promising and increasingly validated avenue to objectively assess (over)hydration is the use of electrical bioimpedance, a technique that has been

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used in various forms (single/multiple frequency and segmental/whole-body bioimpedance) and validated by isotope-dilution methods, accepted reference body composition methods, and techniques that measure relative changes in fluid volumes.[5] In addition, overhydration determined by multiple frequency bioimpedance recently was identified as an important and independent mortality predictor in maintenance HD patients.[6] Bioelectrical impedance analysis (BIA) also has been used successfully to guide HD patients toward normohydration and better BP control.[7]

Despite this increasingly large body of evidence, clinicians are reluctant to adopt bioimpedance-based technologies. This is mainly because of the lack of a definitive randomized controlled trial with hard end points and adequate follow-up demonstrating the superiority of BIA to usual clinical best practice.

The objective of this prospective randomized trial was to compare strict volume control based on bioimpedance versus clinical methods for guiding ultrafiltration prescription in HD patients. In the intervention arm, ultrafiltration goals were derived exclusively from BIA readouts. Most importantly, we investigated the medium-term impact of strict volume control on patient survival, arterial stiffness, and BP values.

METHODS

Study Design

During a 2-month enrollment phase, we considered for inclusion in the trial all adult patients (aged ≥18 years) from the "Dr. C.I. Parhon University Hospital" Dialysis Center already on maintenance HD therapy for more than 3 months (N = 277). Patients with limb amputations, metallic joint prostheses, absence of a permanent vascular access, decompensated cirrhosis, pregnancy, or a cardiac stent or pacemaker were excluded from the study because bioimpedance assessment cannot be performed accurately in such cases. In addition, patients with life expectancy less than 1 year were not considered. The study finally included 131 patients who were eligible and willing to participate, with follow-up of 3.5 years (July 2008 to December 2011). The hospital ethics committee approved the study and all participating patients signed written informed consent.

The final study population of 131 patients fulfilled initial power calculations for detecting a significant difference between groups in pulse wave velocity (PWV) of 1 m/s and in relative fluid overload of 1%. Such a change in PWV and relative fluid overload (computed in regard to mean baseline values of 7.1 m/s and 8.8%, respectively, which were reported previously for HD populations by Covic et al[8] and Wabel et al[9]) would require 60 patients in each arm for 85% power, with 2-tailed $\alpha = 0.05$. At the same time, Wizemann et al[6] previously demonstrated that overhydrated patients have an increased hazard ratio (HR) for death of 2.1. Therefore, in order to show a 50% decrease in mortality from our center's expected death rate of 6% per year,[10] 620 patients in each arm followed up for 2.5 years would have been required (80% power, 2-tailed $\alpha = 0.05$) to be included.[11]

The overall study design is shown in Fig 1A and B. All patients were assigned using the block randomization technique to either the bioimpedance (intervention) group or the clinical-methods (control) group (Fig 1A and B). During the first 2.5 years of the study (the intervention period), dry weight was determined/adjusted in the clinical-methods group by clinical reference criteria (BP value, presence of edema, intradialytic hypotension, cramps etc), whereas in the bioimpedance group, target dry weight was prescribed exclusively based on readouts from the bioimpedance device measurements. The primary end point was all-cause mortality and secondary end points were change in arterial stiffness, BP, and hydration status, assessed at 2.5 years. After this period, during the last year of the study, all patients were left free of any intervention and managed according to the standard medical practice of the dialysis center. At the end of the study, at 3.5 years, a third PWV measurement was performed in all patients.

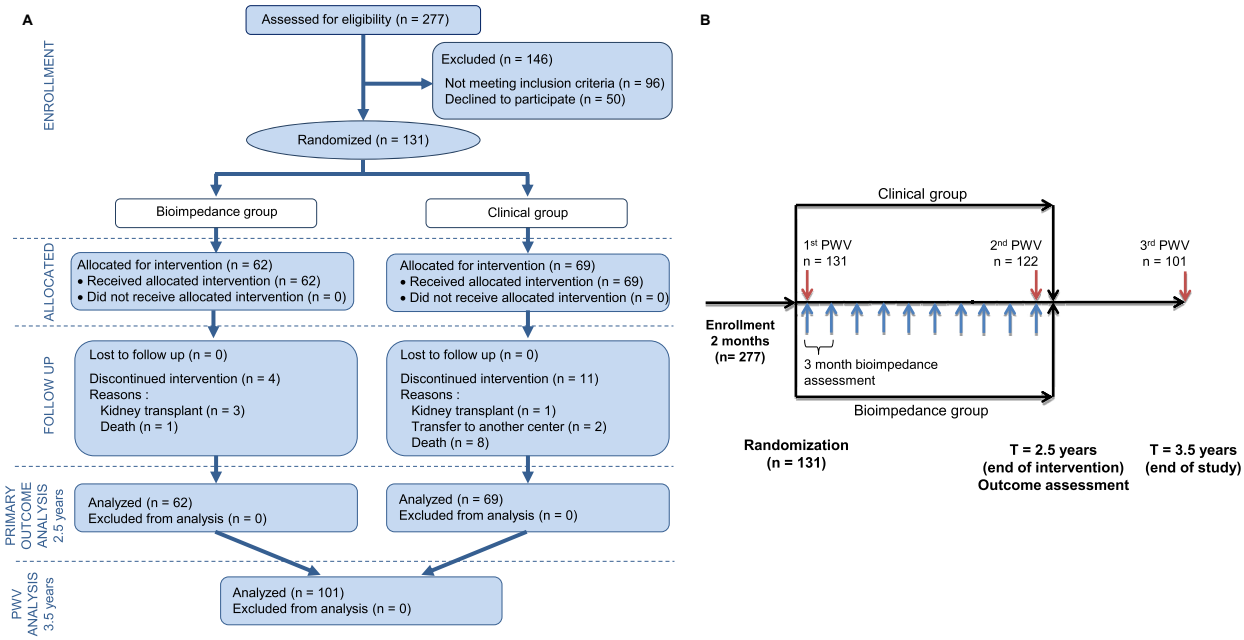

Figure 1. Study (A) flow chart and (B) design. Abbreviation: PWV, pulse wave velocity.