AJKD

Original Investigation

Low-Sodium Versus Standard-Sodium Peritoneal Dialysis Solution in Hypertensive Patients: A Randomized Controlled Trial

*Bolesław Rutkowski, MD, PhD,[1] Paul Tam, MD,[2] Frank M. van der Sande, MD, PhD,[3] Andreas Vychytil, MD,[4] Vedat Schwenger, MD,[5] Rainer Himmele, MD,[6] and Adelheid Gauly, PhD,[7] on behalf of the Low Sodium Balance Study Group**

Background: Peritoneal dialysis (PD) solutions with reduced sodium content may have advantages for hypertensive patients; however, they have lower osmolarity and solvent drag, so the achieved Kt/V_{urea} may be lower. Furthermore, the increased transperitoneal membrane sodium gradient can influence sodium balance with consequences for blood pressure (BP) control.

Study Design: Prospective, randomized, double-blind clinical trial to prove the noninferiority of total weekly Kt/V_{urea} with low-sodium versus standard-sodium PD solution, with the lower confidence limit above the clinically accepted difference of −0.5.

Setting & Participants: Hypertensive patients (≥1 antihypertensive drug, including diuretics, or office systolic BP ≥ 130 mm Hg) on continuous ambulatory PD therapy from 17 sites.

Intervention: 108 patients were randomly assigned (1:1) to 6-month treatments with either low-sodium (125 mmol/L of sodium; 1.5%, 2.3%, or 4.25% glucose; osmolarity, 338-491 mOsm/L) or standard-sodium (134 mmol/L of sodium; 1.5%, 2.3%, or 4.25% glucose; osmolarity, 356-509 mOsm/L) PD solution.

Outcomes: Primary end point: weekly total Kt/V_{urea}; secondary outcomes: BP control, safety, and tolerability.

Measurements: Total Kt/V_{urea} was determined from 24-hour dialysate and urine collection; BP, by office measurement.

Results: Total Kt/V_{urea} after 12 weeks was 2.53 ± 0.89 in the low-sodium group (n = 40) and 2.97 ± 1.58 in the control group (n = 42). The noninferiority of total Kt/V_{urea} could not be confirmed. There was no difference for peritoneal Kt/V_{urea} (1.70 ± 0.38 with low sodium, 1.77 ± 0.44 with standard sodium), but there was a difference in renal Kt/V_{urea} (0.83 ± 0.80 with low sodium, 1.20 ± 1.54 with standard sodium). Mean daily sodium removal with dialysate at week 12 was 1.188 g higher in the low-sodium group ($P < 0.001$). BP changed marginally with standard-sodium solution, but decreased with low-sodium PD solution, resulting in less antihypertensive medication.

Limitations: Broader variability of study population than anticipated, particularly regarding residual kidney function.

Conclusions: The noninferiority of the low-sodium PD solution for total Kt/V_{urea} could not be proved; however, it showed beneficial clinical effects on sodium removal and BP.

INDEX WORDS: Peritoneal dialysis (PD); PD solution; blood pressure; hypertension control; dialysis dose; Kt/V; dialysis adequacy; low-sodium dialysis solution; double-blind; sodium balance; sodium elimination; renal replacement therapy (RRT); randomized controlled trial (RCT).

Peritoneal dialysis (PD) as an established renal replacement therapy should ensure solute clearance, peritoneal ultrafiltration, and the physiologic homeostasis of electrolytes and also maintain acid-base balance. Adequate dialysis is broadly defined in terms of dialysis dose, expressed as Kt/V. In addition, other clinical outcomes deserve attention. For example, effective control of hypertension is of importance

From the [1]Department of Nephrology, Medical University of Gdańsk, Gdańsk, Poland; [2]Scarborough General Hospital, Toronto, Ontario, Canada; [3]Division of Nephrology, Department of Internal Medicine, Maastricht University Medical Center, Maastricht, the Netherlands; [4]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria; [5]Department of Nephrology, University of Heidelberg, Heidelberg, Germany; [6]Fresenius Medical Care North America, Waltham, MA; and [7]Fresenius Medical Care, Bad Homburg, Germany.

[*]A list of the Low Sodium Balance Study Group Investigators appears in the Acknowledgements.

Received October 15, 2014. Accepted in revised form July 27, 2015.

Trial registration: www.clinicaltrialsregister.eu; study number: 2004-002108-14.

Address correspondence to Adelheid Gauly, PhD, Fresenius Medical Care Deutschland GmbH, Else-Kroener-Strasse 1, 61352 Bad Hombur, Germany. E-mail: adelheid.gauly@fmc-ag.com

0272-6386

http://dx.doi.org/10.1053/j.ajkd.2015.07.031

because cardiovascular complications are the most common causes of death in dialysis patients.[1,2]

Serum sodium concentration is considered an important regulatory factor for extracellular volume status and blood pressure (BP) control.[3-8] The potential role of peritoneal sodium elimination in BP control has been described for patients on continuous ambulatory PD (CAPD) therapy.[9] However, the sodium concentration of currently available PD solutions allows only minor diffusive sodium clearance, so that sodium elimination mostly occurs through convection with ultrafiltration. Transperitoneal sodium removal affects total-body sodium balance and extracellular sodium concentration, with subsequent potential reductions of hypervolemia, factors that are pivotal for BP control in patients with chronic kidney disease.[10-13] Using dialysis fluids with low and ultra-low sodium concentrations of 120 and 98 mmol/L, respectively, Nakayama et al showed that low sodium concentrations facilitate diffusive net sodium removal over time.[14,15] In both studies, increased sodium removal led to a decrease in mean arterial BP, whereas no major differences were recorded for body weight and ultrafiltration. Furthermore, enhanced diffusive elimination of sodium may alleviate the dietary restriction of oral salt intake.[16-20] Another study showed benefits in BP, thirst, and fluid status using a glucose-compensated solution with a sodium concentration of 115 mmol/L.[21]

The present study investigates whether a new PD solution with a reduced sodium content of 125 mmol/L enhances diffusive sodium elimination. The slightly reduced osmolarity of the low-sodium solution might also affect ultrafiltration and thereby solute drag; therefore, the possible effect on dialysis dose is worthy of investigation. The objective of the present study was to investigate the therapeutic noninferiority of the new low-sodium solution compared to a standard PD solution using achieved dialysis dose (Kt/V_{urea}) as the primary end point and BP control, safety, and tolerability as secondary end points.

METHODS

Study Design

This was a prospective, controlled, randomized, double-blind, multicenter phase 3 study comparing a low-sodium PD solution with a standard-sodium PD solution (control group). Both solutions were produced by Fresenius Medical Care, Bad Homburg, Germany. A baseline visit was performed just before study start, and further study visits were performed at 2, 6, 12, 18 ± 1, and 25 ± 1 weeks after baseline.

Study Approval and Informed Consent

The trial was conducted in 17 centers: 2 in Austria, 2 in Canada, 1 in Germany, 7 in Poland, and 5 in the Netherlands. The study was approved by the relevant authorities of the participating countries and the institutional review boards of the participating study centers. Informed consent was obtained from each patient prior to inclusion.

Patient Eligibility and Randomization

Eligible patients were 18 years or older, on CAPD therapy for at least 3 months, treated with standard-sodium solution for at least 4 weeks prior to inclusion, and on at least one antihypertensive drug (including diuretics) or showed an office systolic BP ≥ 130 mm Hg. Patients prone to hyponatremia and who had peritonitis within 4 weeks prior to study start were excluded. Detailed eligibility criteria are listed in Item S1 (provided as online supplementary material). Randomization was centrally performed by 1:1 block randomization and was stratified by center.

Treatment Intervention

Patients were randomly assigned to receive CAPD treatment with either the low-sodium (125 mmol/L of sodium) or the standard-sodium solution (134 mmol/L of sodium) for all bags of the day over 6 months in a double-blinded manner. The 2 solutions are identical except for the sodium and chloride content (Table S1). Glucose concentration was not increased to compensate for the lower osmolarity of the low-sodium solution. The individual pre-existing dialysis prescriptions for 1.5%, 2.3%, or 4.25% glucose were maintained during the study unless changed for medical reasons.

Objectives and Outcome Measures

Efficacy

The primary study objective was to assess the noninferiority of the low-sodium solution in comparison to the standard-sodium solution regarding achieved dialysis dose. The primary outcome measure was total weekly Kt/V_{urea} after a 12-week period using the assigned PD solution, assessed using a peritoneal function test.[22] In brief, in order to measure solutes and calculate peritoneal and renal Kt/V (summing up to total Kt/V), dialysate outflow and urine covering 24 hours were collected, the volumes were determined, and a blood sample was taken.

Other efficacy parameters were peritoneal and renal urea clearance, residual kidney function, changes in BP, or changes in the number or dosage of antihypertensive drugs. Glomerular filtration rate (GFR) was calculated as the mean of urea and creatinine clearance, which in turn were determined from urine volume and urine and plasma urea and creatinine concentrations.

Office BP measurements were performed on all study visits as described previously[23]; that is, in a seated position after 5 minutes of rest, with the same arm, and repeated after an interval of 5 minutes. A digital BP device (M5-I or HEM-757 [both Omron]) was used.

Dosing of antihypertensive drugs was based on the defined daily dose (DDD) prescribed at the respective visit (extracted from the Anatomical Therapeutic Chemical/DDD system). One DDD unit reflects the assumed average maintenance dose per day for a drug used for its main indication. Combination drugs without a DDD were split into their components. Furthermore, effects of the low-sodium solution on sodium balance were tested. Daily sodium removal by dialysate was calculated as the sum of the differences of sodium content in the effluents and fresh dialysate for each individual bag used over 24 hours.

Daily sodium intake was assessed using a standard diet protocol. Nutritional and fluid intakes were documented by the patient on 3 consecutive days (2 weekdays and one Sunday or national holiday) and analyzed centrally using validated nutrition software (PRODI 5.0; Nutri-Science GmbH). Psychometric assessments of thirst and desire for salt were performed using a visual analogue scale ranging from 0 (no thirst or desire for salt) to 10 (unsatisfied thirst or desire for salt). Daily ultrafiltration and membrane transporter status (dialysate to plasma concentration of creatinine at 4 hours) were also documented.