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.

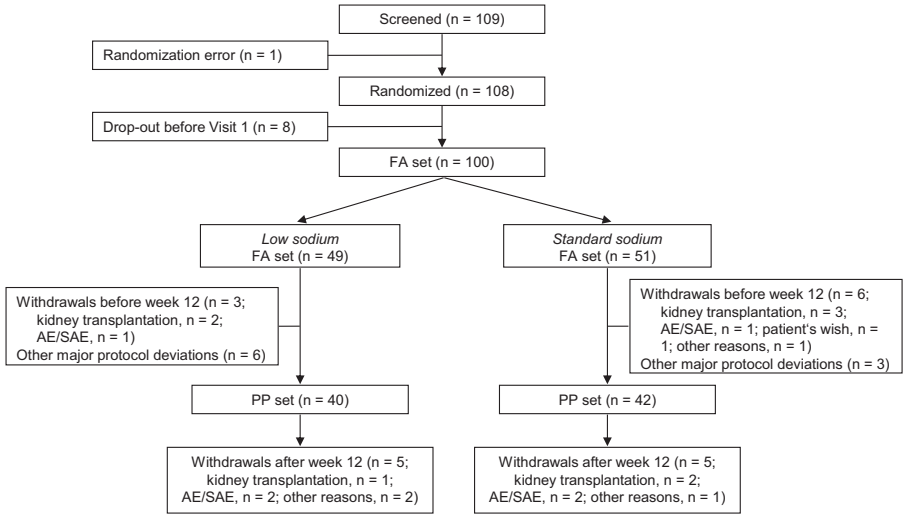

Figure 1. Patient flow in the study. Abbreviations: AE, adverse event; FA, full-analysis; PP, per-protocol; SAE, serious adverse event.

Safety

Target variables for safety were patient withdrawal from the study, treatment-emergent adverse events, adverse events of specific interest (hyponatremia, defined as serum sodium $\leq$ 130 mmol/L, and peritonitis), concomitant medication, abnormal hematology and clinical chemistry measurements, serum sodium concentration, and clinical signs of overhydration.

Sample Size Estimation

Sample size was estimated based on the hypothesis of noninferiority being defined as a clinically acceptable difference in total weekly Kt/V_{urea} of -0.5 with a 1-sided level of significance of 2.5% and 90% power. Clinical acceptability of this difference was based on a previous study showing no effect on mortality.[24] Expecting a slightly smaller mean Kt/V_{urea} at week 12 in the low-sodium group (-0.1) and assuming a common standard deviation of 0.55, a total of 82 patients was needed in the relevant per-protocol population. With an anticipated dropout rate of $\sim$40%, this increased to 120 patients.

Data Collection and Statistical Analysis

For primary analysis, a 2-sided 95% confidence interval was calculated for the difference in least-square means of the total weekly Kt/V_{urea} between groups at week 12 (value for the low-sodium group minus the value for the standard-sodium group). An analysis of covariance (ANCOVA) model was used including adjustment for treatment group, country, and covariate total weekly Kt/V_{urea} at baseline. If the lower confidence limit for total weekly Kt/V_{urea} difference was above the clinically acceptable difference of -0.5, the null hypothesis could be rejected and low sodium could be considered as noninferior.

For secondary variables, group comparisons were performed on a descriptive basis using analogous ANCOVA models for continuous and χ^2 tests for categorical data, both taking the respective values at baseline and other predefined covariates, as appropriate, into account.

Subgroup analysis on patients with GFRs $\leq$ 6 mL/min/1.73 m^2 was performed in a post hoc analysis, but was defined before unblinding. Explorative hypothesis tests were carried out using a 2-sided significance level, α, of 5%. If not stated otherwise, descriptive statistics are given as number and percentage for categorical variables and mean $\pm$ standard deviation for continuous data.

All efficacy analyses are presented for the per-protocol population (no major protocol violation and in study for at least 12 weeks); safety results are presented for the full-analysis set.

All analyses were performed with SAS, version 8.2 (SAS Institute Inc). Sample size calculation was conducted with nQuery Advisor V5.0 (Statistical Solutions Ltd).

RESULTS

Patient Recruitment and Analysis Sets

A total of 109 patients were enrolled, 108 patients were randomly assigned, and 8 patients dropped out before study start due to patient preference (n = 3) or other reasons. The full-analysis set consisted of 49 patients on low-sodium and 51 patients on standard-sodium solution. The per-protocol population (no major protocol violation and on study for at least 12 weeks) comprised 40 patients in the low-sodium and 42 patients in the control group. One patient in each group excluded from the per-protocol group due to protocol violations withdrew after week 12 due to an adverse effect/serious adverse event. Patient flow and reasons for withdrawal from the study are shown in Fig 1.

Baseline Data

Patient characteristics at study inclusion are given in Tables 1 and S2. The 2 groups were comparable regarding demographic and anthropometric data, medical history, and comorbid conditions. Mean baseline GFRs were relatively high in both groups ($>$5 mL/min/1.73 m^2), and some patients had residual kidney function far above the threshold for the recommended initiation of dialysis therapy (maximum observed baseline GFR was $>$30 mL/min/1.73 m^2 in both groups).

Table 1. Patient Characteristics at Baseline According to Dialysate Solution Type

	Low Sodium (n = 49)	Standard Sodium (n = 51)
Age, y	55.0 ± 13.9	55.0 ± 14.8
Male sex	57%	45%
CAPD vintage, mo		
Mean ± SD	20.6 ± 17.8	15.6 ± 14.4
Median [IQR]	11.8 [7.3-34.1]	13.6 [4.1-21.5]
Diabetes types 1 and 2	33%	33%
Hypertension[a]		
Stage I	22%	39%
Stage II	51%	41%
Stage III	27%	16%
Severity grading missing	0%	4%
Systolic BP, mm Hg	150 ± 24	145 ± 22
Diastolic BP, mm Hg	90 ± 14	88 ± 16
Coronary heart disease	27%	26%
Congestive heart failure	6%	2%
Antihypertensive medication, DDD		
Mean ± SD	5.5 ± 5.2	5.5 ± 4.0
Median [IQR]	4.0 [2.3-6.7]	5.0 [2.0-7.8]
Use of diuretics	67%	75%
Body weight, kg	75.3 ± 15.3	71.3 ± 16.1
Residual diuresis, mL/d		
Mean ± SD	846 ± 601	925 ± 844
Median [IQR]	888 [427-1,227]	820 [363-1,463]
GFR, mL/min/1.73 m^2		
Mean ± SD	4.8 ± 6.3	5.3 ± 6.0
Median [IQR]	3.3 [0.9-6.2]	4.2 [1.4-6.5]
Total weekly Kt/V_{urea}	2.58 ± 1.23	2.68 ± 1.13
Peritoneal weekly Kt/V_{urea}	1.67 ± 0.35	1.76 ± 0.43
D/P creatinine[b]	0.67 ± 0.1	0.71 ± 0.11
Ultrafiltration, mL/d		
Mean ± SD	628 ± 595	683 ± 574
Median [IQR]	671 [300-900]	719 [400-1,100]

Note: Full-analysis set (N = 100). Values for categorical variables are given as percentages; values for continuous variables, as mean ± SD or median [IQR].

Abbreviations and definitions: BP, blood pressure; CAPD, continuous ambulatory peritoneal dialysis; DDD, defined daily dose, based on the Anatomical Therapeutic Chemical/DDD system; D/P, dialysate to plasma; GFR, glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

[a]Hypertension stage I, no impairment of vital organs; stage II, partial impairment of vital organs; stage III, damage of vital organs.

[b]At the 4-hour time point.

Primary Efficacy Outcome: Total Weekly Kt/V

The primary efficacy parameter was total weekly Kt/V_{urea} after 12 weeks of treatment. In the per-protocol set, the mean value for total weekly Kt/V_{urea} decreased slightly in the low-sodium group (from 2.69 ± 1.29 to 2.53 ± 0.89) and increased in the control group (from 2.75 ± 1.17 to 2.97 ± 1.58; Fig 2A). The lower 1-sided 97.5% confidence limit for a least-square mean of −0.78 exceeded the clinically acceptable difference (noninferiority margin) of (−) 0.5. Thus, statistical noninferiority of the investigated solution versus the control solution for total weekly Kt/V_{urea} could not be demonstrated (Table 2).

Secondary Efficacy Outcomes

Total Kt/V_{urea} in Patients With GFRs ≤ 6 mL/min/1.73 m^2

A post hoc efficacy analysis in a subgroup of patients with GFRs ≤ 6 mL/min/1.73 m^2 (the recommended threshold for initiating dialysis therapy according to the European Best Practice Guidelines for PD[25]) showed the low-sodium solution to be noninferior to the standard-sodium solution (Table 2).

Peritoneal Kt/V_{urea}

Values for mean peritoneal Kt/V_{urea} were nearly unchanged during the course of the study (Fig 2B). Calculated group differences for the change in peritoneal Kt/V_{urea} were close to zero for all models, with the lower 1-sided 97.5% confidence limit for least-square mean of −0.14.

BP and Antihypertensive Medication

Systolic and diastolic BPs decreased during the course of the study in the low-sodium group, whereas changes in the control group were only marginal (Table 3). The results adjusted for covariates showed a difference in systolic and diastolic BPs at week 12 of 8.6 mm Hg ($P = 0.06$) and 4.6 mm Hg ($P = 0.05$), respectively, lower in the low-sodium group than in the control group.

Because peritoneal membrane transport may affect ultrafiltration and diffusive sodium elimination and in consequence, BP, this was included as a further covariate in an exploratory model. In this model including the baseline ratio of dialysate to plasma creatinine concentrations at the 4-hour time point as an indicator of peritoneal transport status, we found greater BP reduction with the low-sodium solution ($P = 0.03$ and $P = 0.01$ for systolic and diastolic BP, respectively).

Over time, antihypertensive drug treatment increased in both groups. However, the increase was less in the low-sodium group than in the control group (week 12; Table 3). Patients in the low-sodium group required an increase in antihypertensive medication less frequently (20% and 25% at week 12 and 25, respectively) compared with those in the control group (41% and 45% at weeks 12 and 25; χ^2 test: week 12, $P = 0.02$; week 25, $P = 0.04$).

Sodium Balance, Residual Kidney Function, Ultrafiltration, and Clinical Parameters

All descriptive analyses of these parameters are given in Table 3. Adjusted mean daily sodium

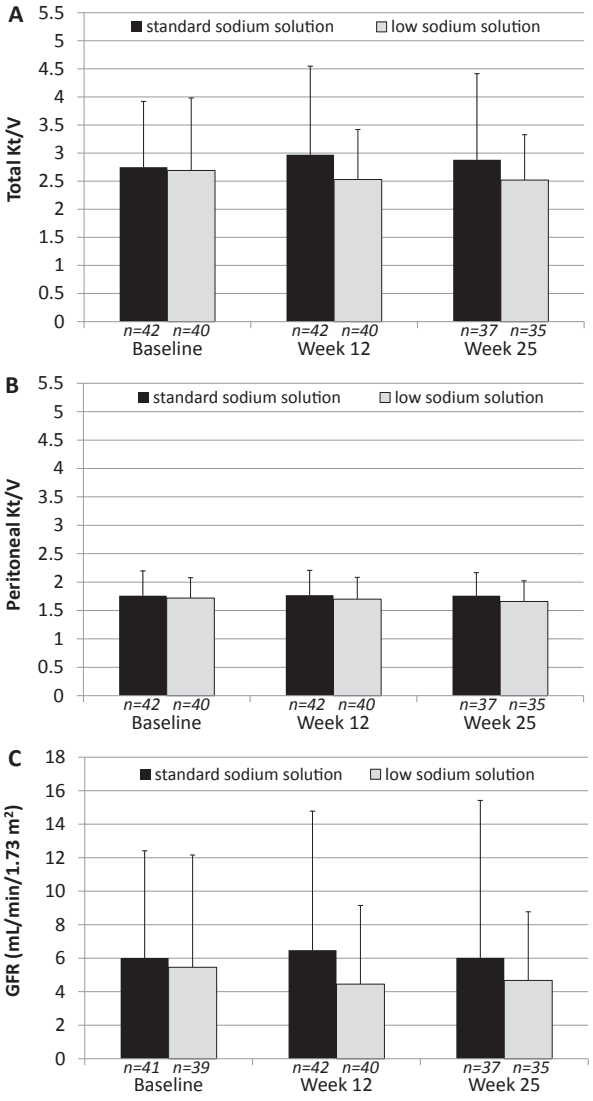

Figure 2. (A) Total weekly Kt/V_{urea}, (B) peritoneal weekly Kt/V_{urea}, and (C) glomerular filtration rate (GFR), all by study group and study visit for the low-sodium and control groups (mean ± standard deviation).

removal with dialysate was significantly higher in the low-sodium group, taking baseline, country, and daily ultrafiltration into account (by 1.188 g [$P < 0.001$] at week 12, by 0.979 g [$P < 0.001$] at week 25, corresponding to ~3 g of sodium chloride at week 12 and 2.5 g at week 25). Mean serum sodium values decreased more in the low-sodium group than in the control group (change of −1.966 mmol/L [$P = 0.005$] at week 12 and −0.799 mmol/L [$P = 0.3$] at week 25). Dietary salt intake did not change.

Thirst decreased in both treatment groups at all visits, but was more pronounced in the low-sodium group ($P = 0.07$ between the treatment groups, week 12). The difference in oral fluid intake was statistically significant at week 25 ($P = 0.02$), but not at week 12 ($P = 0.2$).

Urine production rate was significantly lower at week 12 in the low-sodium group than in the control group (−190.4 mL; $P = 0.03$). However, it increased at week 25 compared to baseline in both groups, with nonsignificant differences between groups. Mean GFR decreased in the low-sodium group, with the group difference of borderline statistical significance at week 12 (−1.87 mL/min/1.73 m^2; $P = 0.05$); no significant difference was seen at week 25 (Fig 2C).

Most patients (low-sodium group, 89.9%; control group, 90.2%) used 4 bags of PD solution per day (equivalent to 8 L). Prescribed glucose concentrations at baseline in the low-sodium and control groups were on average 1.71% ± 0.25% and 1.68% ± 0.30%, respectively, both with no major change throughout the study.

Compared to baseline, mean daily ultrafiltration decreased slightly at weeks 12 and 25 in the low-sodium group, whereas it increased slightly at week 12 and then decreased at week 25 in the control group (Table 3). In the adjusted analysis, the difference between groups was borderline statistically significant at week 12 ($P = 0.05$), but not at week 25.

There were no significant differences between groups for the other efficacy parameters measured (ie, membrane transporter status, psychometric assessments of desire for salt, and nutritional parameters).

Safety Outcome

All safety data refer to the full-analysis set (n = 100). As shown in Table 4, 34 of 49 patients in the low-sodium group and 31 of 51 patients in the control group had 166 treatment-emergent adverse events during the course of the study. Most adverse events reported were mild and generally fully reversible. In the low-sodium group, more patients had treatment-emergent and drug-related adverse events (mostly hyponatremia and peripheral edema) than in the control group.

Five patients in the low-sodium group and 4 patients in the control group each had 6 adverse events that led to permanent discontinuation of study medication. In the control group, more patients had adverse events that were classified as severe, serious, or fatal. Twenty-six patients had a total of 40 serious adverse events: 15 occurred in the low-sodium group and 25 in the control group. Of these serious adverse events, 3 deaths occurred during the course of the trial, one in the low-sodium group (exacerbation of coronary heart disease) and 2 in the control group (peritonitis/colon carcinoma and peritonitis); all 3 were judged as unlikely to be related or not related to trial medication.

Table 2. Total, Peritoneal, and Renal Kt/V_{urea} for Per-Protocol Population and Analyzed by GFR

	Per-Protocol Population		Population With Baseline GFR ≤ 6 mL/min/1.73 m^2		Population With Baseline GFR > 6 mL/min/1.73 m^2	
	Low Sodium (n = 40)	Standard Sodium (n = 42)	Low Sodium (n = 26)	Standard Sodium (n = 26)	Low Sodium (n = 14)	Standard Sodium (n = 16)
Total Kt/V_{urea}						
Baseline	2.69 ± 1.29	2.75 ± 1.17	2.11 ± 0.36	2.23 ± 0.48	3.76 ± 1.68	3.58 ± 1.47
Wk 12	2.53 ± 0.89	2.97 ± 1.58	2.12 ± 0.53	2.39 ± 0.56	3.29 ± 0.93	3.91 ± 2.18
Group difference at wk 12 (95% CI)	−0.396 (−0.780 to −0.012)		−0.200 (−0.473 to 0.074)		−0.751 (−1.732 to 0.230)	
Peritoneal Kt/V_{urea}						
Baseline	1.72 ± 0.36	1.76 ± 0.44	1.67 ± 0.33	1.77 ± 0.42	1.81 ± 0.40	1.74 ± 0.48
Wk 12	1.70 ± 0.38	1.77 ± 0.44	1.68 ± 0.38	1.76 ± 0.40	1.72 ± 0.40	1.78 ± 0.51
Group difference at wk 12 (95% CI)	−0.038 (−0.141 to 0.066)		−0.011 (−0.116 to 0.137)		−0.124 (−0.320 to 0.072)	
Renal Kt/V_{urea}						
Baseline	0.97 ± 1.24	0.99 ± 1.17	0.45 ± 0.34	0.46 ± 0.40	1.95 ± 1.66	1.84 ± 1.50
Wk 12	0.83 ± 0.80	1.20 ± 1.54	0.43 ± 0.39	0.63 ± 0.52	1.57 ± 0.86	2.12 ± 2.14
Group difference at wk 12 (95% CI)	−0.355 (−0.697 to −0.014)		−0.182 (−0.393 to 0.028)		−0.639 (−1.540 to 0.262)	

Note: Peritoneal weekly Kt/V was calculated as the (sum of urea clearance of all bags of day) × 7/urea distribution volume. Renal weekly Kt/V was calculated as (renal urea clearance/urea distribution volume) × 7 × 1.44. Total weekly Kt/V is the sum of peritoneal weekly Kt/V and renal weekly Kt/V. Unless otherwise indicated, values are mean ± standard deviation.

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate.

Six events of hyponatremia in 3 patients of the low-sodium group were reported. Four further events (3 in the low-sodium and one in the control group) of hyponatremia with sodium levels of exactly 130 mmol/L were noted. These events were categorized as mild or moderate, and all resolved by the end of the study. In the low-sodium group, a reduction in serum sodium level from baseline to week 12 (mean change of −2.54 mmol/L) and to week 25 (mean change of −2.16 mmol/L) was observed, whereas there was almost no change in the control group at either of these visits (−0.03 and −0.56 mmol/L, respectively). All other biochemical parameters showed no significant changes from baseline or between groups. Vital signs and clinical examinations did not raise safety concerns. None of the patients showed serious signs of overhydration or relevant changes in body weight during the study.

DISCUSSION

The present study investigated whether a PD solution with reduced sodium content provides a dialysis dose (total weekly Kt/V_{urea}) comparable to that of a standard PD solution. Noninferiority of the low-sodium solution in comparison to the standard solution could not be established for total Kt/V_{urea}. Whereas a standard deviation of 0.55 was assumed for sample size calculation, results showed a standard deviation between 0.9 and 1.6 at week 12. Nonetheless, the mean total weekly Kt/V_{urea} (2.53 in the low-sodium and 2.97 in the control group after 12 weeks) was clearly above the target of a total weekly Kt/V_{urea} ≥ 1.7, as defined by current guidelines.[25,26]

The changes in total Kt/V_{urea} may be explained by differences in residual kidney function between groups, which in turn seemed to be related to high residual kidney function in certain patients. Approximately one-third of the patients had GFRs > 6 mL/min/1.73 m^2 at baseline; extreme GFRs as high as 56.5 mL/min/1.73 m^2 were also recorded in the course of the study. Although some patients had cardiac insufficiency (New York Heart Association class I or II), which is a possible reason to initiate dialysis therapy earlier than commonly recommended, this does not fully explain why that many patients with high GFRs were initiated on dialysis therapy. In these patients, changes in total Kt/V_{urea} are greatly influenced by the changes in kidney function. This is supported because noninferiority of the low-sodium solution was shown for the per-protocol subgroup of patients with GFRs ≤ 6 mL/min/1.73 m^2. Separate analysis of peritoneal Kt/V_{urea} showed that the actual dialysis dose achieved with the 2 PD solutions was nearly identical, with standard deviations lower than 0.5, as anticipated.

Residual kidney function and ultrafiltration were significantly lower in the low-sodium group after 3 months, but not after 6 months. Although the slightly lower osmolarity of the solution under investigation could explain the reduced ultrafiltration, one would then expect that diuresis should increase due to an increase in vascular fill volume. However, the decrease

Table 3. BP Parameters and Sodium and Fluid Status

	Low-Sodium Solution			Standard-Sodium Solution		
	Baseline	Wk 12	Wk 25	Baseline	Wk 12	Wk 25
No. of patients	40	40	35	42	42	37
Systolic BP, mm Hg	152 ± 24	141 ± 22	143 ± 23	148 ± 21	147 ± 23	144 ± 23
Diastolic BP, mm Hg	91 ± 14	86 ± 11	85 ± 13	90 ± 14	90 ± 13	88 ± 15
Antihypertensive medication, DDD						
Mean ± SD	5.3 ± 5.2	5.7 ± 5.4	6.0 ± 5.4	5.6 ± 3.9	6.6 ± 3.8	6.3 ± 3.7
Median [IQR]	3.7 [2.3-6.7]	4.5 [2.1-7.6]	4.7 [2.2-8.3]	5.3 [2.0-7.5]	6.1 [3.5-8.0]	6.0 [3.0-7.8]
Mean glucose applied, %	1.74 ± 0.27	1.75 ± 0.31	1.69 ± 0.26	1.67 ± 0.29	1.70 ± 0.30	1.67 ± 0.25
Peritoneal ultrafiltration, mL/24 h	657 ± 569	602 ± 707	621 ± 520	698 ± 548	741 ± 664	640 ± 676
Urine volume, mL/24 h						
Mean ± SD	915 ± 594	868 ± 660	1,022 ± 700	977 ± 858	1,081 ± 808	1,015 ± 791
Median [IQR]	902 [541-1,303]	893 [416-1,313]	890 [513-1,537]	835 [455-1,463]	1,000 [522-1,600]	930 [588-1,300]
GFR, mL/min/1.73 m^2						
Mean ± SD	5.46 ± 6.75	4.45 ± 4.69	4.67 ± 4.12	6.01 ± 6.39	6.48 ± 8.32	6.02 ± 9.36
Median [IQR]	3.79 [1.20-6.34]	3.91 [0.70-6.44]	4.05 [1.71-6.72]	4.47 [2.01-7.31]	4.64 [2.52-7.85]	3.57 [2.55-6.11]
Sodium removal urine, g/d	1.86 ± 1.35	1.79 ± 1.96	1.99 ± 1.88	2.22 ± 3.50	2.04 ± 2.10	2.09 ± 2.38
Sodium removal dialysate, g/d	3.10 ± 1.92	2.71 ± 2.13	2.67 ± 1.66	1.68 ± 1.65	1.75 ± 2.05	1.32 ± 2.02
Serum sodium, mEq/L	140.2 ± 3.03	137.8 ± 3.59	138.3 ± 3.95	139.6 ± 3.53	139.4 ± 2.83	138.4 ± 3.30
Thirst, mm on VAS	46.7 ± 22.8	30.4 ± 25.4	32.2 ± 23.4	50.3 ± 23.7	41.4 ± 28.0	39.8 ± 28.9
Desire for salt, mm on VAS	27.1 ± 19.4	23.6 ± 25.3	22.2 ± 21.5	26.2 ± 19.3	26.8 ± 20.9	24.2 ± 19.4
No. of patients	23	28	29	27	32	30
Dietary water intake, mL/d	1,400 ± 751	1,167 ± 515	995 ± 463	1,138 ± 503	1,123 ± 499	1,052 ± 554
Dietary salt intake, g/d	2.41 ± 1.40	2.64 ± 1.69	2.77 ± 1.17	2.36 ± 0.98	2.37 ± 1.14	2.24 ± 1.27

Note: All data are derived from the per-protocol population. Values are given as mean ± SD or median [IQR].

Abbreviations and definitions: BP, blood pressure; DDD, defined daily dose based on the Anatomical Therapeutic Chemical/DDD system; GFR, glomerular filtration rate; IQR, interquartile range; SD, standard deviation; VAS, visual analogue scale ranging from 0 (no thirst, no desire for salt) to 100 mm (unquenchable thirst or desire for salt).

in serum sodium level might result in lower thirst and fluid intake, potentially reducing fluid overload and, in turn, urine excretion, as shown in studies with pure salt restriction[27] or as regularly seen in incident dialysis patients. Hypervolemia and high BP are closely associated with sodium uptake and sodium balance.[27] Treatment with the reduced-sodium PD solution showed increased sodium elimination by the peritoneal membrane, in line with results from a study using a similarly composed low-sodium PD solution.[28] This results in decreased serum sodium levels, systolic BP, and diastolic BP, as well as antihypertensive medication dosage. Our results are consistent with findings from studies that used different sodium concentrations and prescription schedules.[14,15,21] Unfortunately, bioimpedance data were not available for assessment of hydration status, analysis of how this may be influenced by the low-sodium solution, and whether it affects efficacy and safety outcomes.

In comparison to some studies, the sodium concentration we used (125 mmol/L) is very moderate in terms of reduced-sodium dialysate solutions. This low-sodium solution was designed for continuous use in all daily exchanges. This avoids physiologic fluctuations caused by alternating normal- and low-sodium exchanges, as seen in other trials using lower sodium concentrations but restricting use to one bag per day. We did not observe any clinically relevant adverse effects related to ultrafiltration despite not compensating for the decrease in total osmolarity. Such compensation seems to be necessary for solutions with sodium content of 115 or 102 mmol/L, as previously described.[21]

Ultrafiltration, volume status, and BP are related to peritoneal transport properties.[29] Because high transporters tend to have lower ultrafiltration when treated with CAPD, an improved potential for diffusive

Table 4. Summary of Adverse Events According to Solution Type

	Low Sodium (n = 49)	Standard Sodium (n = 51)
General		
TEAEs	94	72
Severe AEs	4	9
Drug related AEs[a]	15	2
AEs that led to solution discontinuation	6	6
Serious AEs[b]	15	25
Deaths	1	2
TEAEs accounting for ≥5% of TEAEs in either group		
Peritonitis	5	11
Peripheral edema	5	3
Catheter-related infection	0	4
Decrease in hemoglobin	3	4
Hyponatremia (≤130 mmol/L)	9	1
Drug-related AEs[a]		
Peripheral edema	4	0
Hyponatremia	6	0
Hypokalemia	2	0
Fluid retention	0	1
Restless leg syndrome	1	0
Hoarseness	1	0
Hypotension	1	0
Orthostatic hypotension	0	1

Note: Full-analysis set (N = 100).

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

[a]Relationship probable or possible.

[b]AEs leading to death, hospitalization, or serious deterioration in health status.

sodium removal might compensate for the lower convective removal. This could explain why the effect of the low-sodium solution on BP is even more pronounced when peritoneal permeability is taken into account.

Both solutions showed a good general safety profile. As expected, more adverse events with hyponatremia were seen in the low-sodium group, all of which were judged to be mild or moderate and had resolved by the end of the study. These results suggest that hyponatremia may occur with the use of a low-sodium CAPD solution and thus sodium should be closely monitored, particularly in conjunction with actual residual kidney function. Use of a low-sodium solution for only part of the daily prescribed bags allows flexible adjustment according to the patient's individual needs.

Several limitations of the study should be acknowledged. Unexpectedly, our study population showed broader variability than published clinical data. This could have been accounted for by a larger sample size or more stringent exclusion criteria. Furthermore, peritoneal Kt/V_{urea} could have been considered as a primary end point instead of total Kt/V_{urea} in order to directly evaluate the dose provided by the PD solution.

In conclusion, a PD solution with a reduced sodium content of 125 mmol/L was investigated for its ability to provide adequate dialysis and to improve BP control in PD patients. Although results of the study did not show statistical proof of noninferiority for the primary efficacy parameter total Kt/V_{urea} due to variability of residual kidney function, noninferiority was demonstrated for patients with GFRs $\leq$ 6 mL/min/1.73 m^2 and for peritoneal clearances. With respect to sodium removal and BP control, a significant improvement could be seen with the low-sodium PD solution. Evaluation of safety parameters revealed that treatment with the new solution was safe and well tolerated. Low-sodium PD solutions may be a viable alternative to standard solutions for hypertensive long-term PD patients.

ACKNOWLEDGEMENTS

We acknowledge the commitment and dedication of the study investigators and their clinical teams at the participating centers during the trial: V. Schwenger, University of Heidelberg, Germany; A. Vychytil, Medical University of Vienna, Austria; G. Kopriva, Wilhelminenspital der Stadt Wien, Vienna, Austria; F.M. van der Sande, Maastricht University Medical Center, the Netherlands; C.J.A.M. Konings, Catharina Ziekenhuis, Eindhoven, the Netherlands; P.L. Rensma, St. Elisabeth Ziekenhuis, Tilburg, the Netherlands; M. van Buren, Haga Ziekenhuis, locatie Leyenburg, Den Haag, the Netherlands; L.J. Vleming, Haga Ziekenhuis, locatie Rode Kruis, Den Haag, the Netherlands; A. Książek, Akademia Medyczna Szpital Kliniczny, Lublin, Poland; M. Klinger, Akademia Medyczna Szpital Kliniczny, Wrocław, Poland; B. Rutkowski, Akademia Medyczna Gdańska, Gdańsk, Poland; M. Myśliwiec, Akademia Medyczna Wojewódzki Szpital Specjalistyczny, Białystok, Poland; M. Nowicki, Uniwersytet Medyczny, Szpital Kliniczny, Łódź, Poland; W. Sułowicz, Uniwersytet Jagielloński Collegium Medicum, Kraków, Poland; W. Grzeszczak, Samodzielny Publiczny Szpital Kliniczny, Slaskiej Akademia Medyczna w Katowicach, Zabrze, Poland; P. Tam, Scarborough General Hospital, Scarborough, Ontario, Canada; and D. Ouimet, Hopital Mainsonneuve Rosemont, Montréal, Québec, Canada.

Part of this study was presented at the 11th Congress of the International Society for Peritoneal Dialysis, Hong Kong, August 25-29, 2006.

Support: The clinical trial was funded by Fresenius Medical Care. The sponsor was involved in the study design; data collection, analysis, and interpretation; preparation of study report; and preparation of the manuscript.

Financial Disclosure: Dr Vychytil has received consulting and lecture fees and travel funding (unrelated to this trial) from Baxter, Fresenius Medical Care, and Gambro and been a principal investigator in trials funded by Baxter and Fresenius Medical Care. Dr Rutkowski has received consulting and lecture fees (unrelated to this trial) from Fresenius Medical Care and has been a principal investigator in trials funded by Fresenius. Drs Himmele and Gauly are fulltime employees at Fresenius Medical Care. Dr Schwenger has received lecture fees and scientific funding (unrelated to this trial) from Baxter, Fresenius Medical Care, and Gambro. The other authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: RH, AG; data acquisition: BR, PT, FMvdS, AV, VS; data interpretation: all

authors. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. AG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Composition of investigational and control PD solution.

Table S2: Patient characteristics at baseline, per-protocol set.

Item S1: Eligibility criteria.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.07.031) is available at www.ajkd.org

REFERENCES

1. Colombi A. Sodium modelling in CAPD. *Contrib Nephrol*. 1991;89:155-160.

2. Lameire N, Vanholder RC, Van LA, et al. Cardiovascular diseases in peritoneal dialysis patients: the size of the problem. *Kidney Int Suppl*. 1996;56:S28-S36.

3. Gault MH, Ferguson EL, Sidhu JS, Corbin RP. Fluid and electrolyte complications of peritoneal dialysis. Choice of dialysis solutions. *Ann Intern Med*. 1971;75(2):253-262.

4. Prichard S, Sniderman A, Cianflone K, Marpole D. Cardiovascular disease in peritoneal dialysis. *Perit Dial Int*. 1996;16(suppl 1):S19-S22.

5. Chatoth DK, Golper TA, Gokal R. Morbidity and mortality in redefining adequacy of peritoneal dialysis: a step beyond the National Kidney Foundation Dialysis Outcomes Quality Initiative. *Am J Kidney Dis*. 1999;33(4):617-632.

6. Messerli FH, Schmieder RE, Weir MR. Salt. A perpetrator of hypertensive target organ disease? *Arch Intern Med*. 1997;157(21):2449-2452.

7. MacGregor GA. Salt—more adverse effects. *Am J Hypertens*. 1997;10(5, pt 2):37S-41S.

8. Charra B. Fluid balance, dry weight, and blood pressure in dialysis. *Hemodial Int*. 2007;11(1):21-31.

9. Ates K, Nergizoglu G, Keven K, et al. Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. *Kidney Int*. 2001;60(2):767-776.

10. Flanigan MJ, Khairullah QT, Lim VS. Dialysate sodium delivery can alter chronic blood pressure management. *Am J Kidney Dis*. 1997;29(3):383-391.

11. De Vecchi AF. Adequacy of fluid/sodium balance and blood pressure control. *Perit Dial Int*. 1994;14(suppl 3):S110-S116.

12. Fine A, Fontaine B, Ma M. Commonly prescribed salt intake in continuous ambulatory peritoneal dialysis patients is too restrictive: results of a double-blind crossover study. *J Am Soc Nephrol*. 1997;8(8):1311-1314.

13. Wang T, Waniewski J, Heimburger O, Werynski A, Lindholm B. A quantitative analysis of sodium transport and removal during peritoneal dialysis. *Kidney Int*. 1997;52(6):1609-1616.

14. Nakayama M, Kawaguchi Y, Yokoyama K, et al. Antihypertensive effect of low Na connection (120 mEq/l) solution for CAPD patients. *Clin Nephrol*. 1994;41(6):357-363.

15. Nakayama M, Yokoyama K, Kubo H, et al. The effect of ultra-low sodium dialysate in CAPD. A kinetic and clinical analysis. *Clin Nephrol*. 1996;45(3):188-193.

16. Horiuchi T, Sumida Y. Mechanism of water and sodium removal in CAPD with low sodium dialysate (LNaD). *J Jpn Soc Dial Ther*. 1996;29:87-96.

17. Imholz AL, Koomen GC, Struijk DG, Arisz L, Krediet RT. Fluid and solute transport in CAPD patients using ultralow sodium dialysate. *Kidney Int*. 1994;46(2):333-340.

18. Leypoldt JK, Charney DI, Cheung AK, Naprestek CL, Akin BH, Shockley TR. Ultrafiltration and solute kinetics using low sodium peritoneal dialysate. *Kidney Int*. 1995;48(6):1959-1966.

19. Krautzig S, Janssen U, Koch KM, Granolleras C, Shaldon S. Dietary salt restriction and reduction of dialysate sodium to control hypertension in maintenance haemodialysis patients. *Nephrol Dial Transplant*. 1998;13(3):552-553.

20. Locatelli F, Di Filippo S, Manzoni C. Sodium kinetics during dialysis. *Semin Dial*. 1999;12(suppl):S41-S44.

21. Davies S, Carlsson O, Simonsen O, et al. The effects of low-sodium peritoneal dialysis fluids on blood pressure, thirst and volume status. *Nephrol Dial Transplant*. 2009;24(5):1609-1617.

22. Keen ML, Gotch FA. Peritoneal function test as a basis for assessment of adequate therapy and for urea kinetic modelling. *Nieren Hochdruckkrankh*. 1994;23(suppl 2):S141-S143.

23. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252.

24. Paniagua R, Amato D, Vonesh E, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol*. 2002;13(5):1307-1320.

25. Dombros N, Dratwa M, Feriani M, et al. European best practice guidelines for peritoneal dialysis. 7 Adequacy of peritoneal dialysis. *Nephrol Dial Transplant*. 2005;20(suppl 9):ix24-ix27.

26. Peritoneal Dialysis Adequacy 2006 Work Group. Clinical practice guidelines for peritoneal adequacy, update 2006. *Am J Kidney Dis*. 2006;48(suppl 1):S91-S97.

27. Gunal AI, Duman S, Ozkahya M, et al. Strict volume control normalizes hypertension in peritoneal dialysis patients. *Am J Kidney Dis*. 2001;37(3):588-593.

28. Nakayama M, Kasai K, Imai H, on behalf of the TRM-280 Study Group. Novel low Na peritoneal dialysis solutions designed to optimize Na gap of effluent: kinetics of Na and water removal. *Perit Dial Int*. 2009;29(5):528-535.

29. Tonbul Z, Altintepe L, Sozlu C, Yeksan M, Yildiz A, Turk S. The association of peritoneal transport properties with 24-hour blood pressure levels in CAPD patients. *Perit Dial Int*. 2003;23(1):46-52.