HYDRATION STATUS OF PATIENTS DIALYZED WITH BIOCOMPATIBLE PERITONEAL DIALYSIS FLUIDS

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◆ **Background:** Biocompatible fluids for peritoneal dialysis (PD) have been introduced to improve dialysis and patient outcome in end-stage renal disease. However, their impact on hydration status (HS), residual renal function (RRF), and dialysis adequacy has been a matter of debate. The aim of the study was to evaluate the influence of a biocompatible dialysis fluid on the HS of prevalent PD patients.

◆ **Methods:** The study population consisted of 18 prevalent PD subjects, treated with standard dialysis fluids. At baseline, 9 patients were switched to a biocompatible solution, low in glucose degradation products (GDPs) (Balance; Fresenius Medical Care, Bad Homburg, Germany). Hydration status was assessed through clinical evaluation, laboratory parameters, echocardiography, and bioimpedance spectroscopy over a 24-month observation period.

◆ **Results:** During the study period, urine volume decreased similarly in both groups. At the end of the evaluation, there were also no differences in clinical (body weight, edema, blood pressure), laboratory (N-terminal pro-brain natriuretic peptide, NTproBNP), or echocardiography determinants of HS. However, dialysis ultrafiltration decreased in the low-GDP group and, at the end of the study, equaled 929 ± 404 mL, compared with $1,317 \pm 363$ mL in the standard-fluid subjects ($p = 0.06$). Hydration status assessed by bioimpedance spectroscopy was $+3.64 \pm 2.08$ L in the low-GDP patients and $+1.47 \pm 1.61$ L in the controls ($p = 0.03$).

◆ **Conclusions:** The use of a low-GDP biocompatible dialysis fluid was associated with a tendency to overhydration, probably due to diminished ultrafiltration in prevalent PD patients.

biocompatible fluids are characterized by a neutral or nearly neutral pH, low concentration of glucose degradation products (GDPs), and, in some cases, bicarbonates instead of lactate used as a buffer. However, the initial enthusiasm has recently given way to more or less pronounced skepticism as studies evaluating biocompatible solutions have produced conflicting results as to the hydration status (HS) of treated patients, the preservation of residual renal function (RRF), and the risk of dialysis-related peritonitis (1). Given these uncertainties, the present study was undertaken to assess the impact of a biocompatible dialysis fluid on the HS of PD subjects.

METHODS

STUDY POPULATION

The study was a single-center prospective evaluation that included 18 adult prevalent PD patients. Exclusion criteria were as follows: dialysis-related complications within the 8 weeks preceding the analysis, more than 2 peritonitis episodes within 6 months prior to baseline, presence of an implantable cardioverter-defibrillator, a pacemaker, or a coronary stent, and limb amputations. All patients were initially dialyzed with a standard glucose-based dialysis fluid (stay•safe; Fresenius, Bad Homburg, Germany). Nine subjects were transferred to a low-GDP biocompatible fluid (Balance; Fresenius Medical Care, Bad Homburg, Germany) at baseline, the other 9 remained on the previous dialysis prescription. The observation period was 24 months. All the patients were treated with 1.5% glucose fluids, 4 exchanges per day, throughout the evaluation period. The causes of primary kidney disease in patients switched to the low-GDP fluids were primary glomerulonephritis in 4 patients, diabetic nephropathy in 3 cases, lupus nephritis in 2 subjects, and vasculitis in 1 patient. In the control group, they were primary glomerulonephritis in 5 subjects, diabetic nephropathy in 3 patients, hypertensive nephropathy in 1 case, and autosomal dominant polycystic kidney disease in 1 patient. All of them were diagnosed with arterial hypertension and received medication, including low-dose angiotensin-converting-enzyme (ACE)-inhibitor in every patient. Prescribed medication did not change during the study. The patients received 120–160 mg of furosemide daily; its use did not differ between the groups and did not change during the study. Informed consent

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Peritoneal dialysis (PD) is among the major methods of renal replacement therapy. Since the times of Georg Ganter, who first attempted PD to treat a patient with kidney disease in 1923, there has been a continuous search for an optimal dialysis fluid that would be both effective and safe. The introduction of so-called biocompatible fluids seemed to be a major step in this quest. In comparison with standard dialysis fluids,

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was obtained from each patient. The local ethics committee approved the study protocol.

ASSESSMENT OF HYDRATION STATUS

The assessment of patients' hydration status (HS) included a physical examination, data on body weight, systolic and diastolic blood pressure, dialysis ultrafiltration, and urine volume. Furthermore, a bioimpedance spectroscopy was performed with a Body Composition Monitor (BCM) (Fresenius Medical Care, Bad Homburg, Germany). The analysis included evaluation of total body water (TBW), extracellular water (ECW), intracellular water (ICW), and HS. The physical examination and bioimpedance analysis were performed at baseline, and at months 6, 12, and 24 of the study period.

A detailed echocardiography analysis was done at baseline, and at 1 year and 2 years of observation. It was performed with a Philips 11XE Ultrasound System (Amsterdam, The Netherlands) and included a 2D assessment of the aorta and left atrium and an M-mode evaluation of the left ventricle. The parameters assessed included left ventricular end-diastolic diameter (LVD), left ventricular systolic diameter (LVS), stroke volume index (SVI), cardiac index (CI), inferior vena cava (IVC), left atrial volume (LAV), as well as blood flow patterns: early wave of mitral inflow, atrial wave of mitral inflow, systolic wave of pulmonary vein flow, diastolic wave of pulmonary vein flow, and atrial reversal of pulmonary vein flow.

LABORATORY ANALYSIS

Laboratory parameters were analyzed at baseline, as well as at months 6, 12, and 24. They included serum C-reactive protein (CRP), prealbumin, N-terminal pro B-type natriuretic peptide (NTproBNP), urea, creatinine, calcium and phosphate, as well as hemoglobin concentration. Dialysis adequacy was estimated with a weekly urea Kt/V, and peritoneal transport on the basis of a standard peritoneal equilibration test (PET).

STATISTICAL ANALYSIS

Results are expressed as mean and standard deviation or median and interquartile range, as appropriate. The assumption of normality was verified with the Kolmogorov-Smirnov test. A p value < 0.05 was considered statistically significant. Comparisons between the 2 groups were assessed with a Student's unpaired t -test, or Mann-Whitney test, as appropriate. The changes in parameters measured during consecutive visits were compared with the use of the repeated measures analysis of variance. The statistical analysis was performed using statistical software Statistica version 7.1 (StatSoft Inc., Tulsa, OK, USA).

RESULTS

Out of 18 patients evaluated, all attended the first control visit at month 6, 2 were lost to follow-up before the second

visit at month 12, and a further 2 were lost before the third visit at month 24 (in both cases, 1 from the low-GDP group due to peritonitis, and the other from the standard fluid group, due to renal transplantation). There were no other peritonitis episodes in the studied groups during the evaluation period. Baseline characteristics of the studied patients are shown in Table 1. The subjects from the group converted to the low-GDP biocompatible fluid were, on average, slightly older and with a longer time on dialysis, although these differences were of no statistical significance.

Throughout the observation period, urine volume decreased in both groups. The percentage decrease in the control group equaled $40 \pm 29\%$, while in the patients dialyzed with the low-GDP fluid, it was $30 \pm 26\%$. The difference in urine volume decline was not significant between the groups. Similarly, the urine volume assessed at the end of the study (24 months) was comparable in both groups of patients.

The ultrafiltration remained fairly stable throughout the study in patients treated with standard fluids, while it declined in the subjects on low-GDP solutions (Figure 1). At the end of the study, the mean ultrafiltration in the standard fluid group was $1,317 \pm 363$ mL, and in patients dialyzed with the low-GDP solution, it was 929 ± 404 mL ($p = 0.06$). It should be noted that the dialysate/plasma (D/P) creatinine ratio did not change substantially during the evaluation period.

The clinical indices of HS (body weight, presence of edema, systolic, and diastolic blood pressure) did not differ between the groups (data not shown). Dialysis adequacy did not change significantly during the evaluation, as at the end of observation period, the urea Kt/V was 2.26 ± 0.55 in patients who stayed on standard fluids and 2.18 ± 0.38 in the low-GDP group. Similarly, there were no significant differences in the laboratory parameters assessed (hsCRP, NTproBNP, prealbumin) between the baseline and the completion of the study, or between the analyzed groups. The NTproBNP at the end of the study was 79.9 ± 64.7 pg/mL in patients dialyzed with

TABLE 1
Baseline Characteristics of the Studied Patients

	Stay-safe (n=9)	Balance (n=9)	P value
Age (years)	45.0 (38.0–50.0)	53.0 (43.6–62.0)	0.12
Gender (%M)	44	56	0.7
D/P	0.59±0.08	0.66±0.11	0.1
Time on dialysis (months)	16.4±12.2	26.6±13.1	0.1
Kt/V	2.34±0.45	2.36±0.63	0.91
RRF (mL)	1,117±693	1,133±1,119	0.97
NTproBNP (pg/mL)	97.5±92.6	83.0±79.0	0.72
hsCRP (mg/L)	7.96±9.09	8.72±8.00	0.84
Prealbumin (mg/dL)	31.6±5.8	34.1±4.9	0.32

M = male; RRF = residual renal function; D/P = dialysate/plasma; RRF = residual renal function; NTproBNP = N-terminal pro-brain natriuretic peptide; hsCRP = high-sensitivity C-reactive protein.

standard fluids and 58.3 ± 35.3 pg/mL in subjects treated with low-GDP dialysis ($p =$ not significant). The echocardiography assessment revealed no differences in the cardiac parameters between the groups, nor in those associated with HS, such as LVS, LVD, LAV, or IVC.

The bioimpedance spectroscopy showed that HS remained fairly stable in the control patients, with a 0.46-L decrease in the mean, while it increased by 1.53 L in subjects treated with Balance (Figure 2). At the end of the study, the mean HS in the standard-fluid group was 1.47 ± 1.61 L, while it reached 3.64 ± 2.08 L in the low-GDP patients ($p = 0.03$). The difference in HS was probably due mainly to changes in ECW, which increased in the low-GDP group from 18.1 ± 3.6 L to 19.2 ± 3.4 L, while it remained stable in the control patients (17.7 ± 3.4 at the beginning and 17.6 ± 3.5 L at the end of evaluation) (Figure 3a). The ICW remained unchanged during the 2 years of the study period. The initial values were 19.7 ± 4.5 L in the low-GDP subjects, and 18.8 ± 2.9 L in controls and, after 24 months, 18.9 ± 4.0 L, and 19.0 ± 3.3 L, respectively

Figure 1 — Dialysis ultrafiltration values in patients treated with fluids characterized by low concentration of glucose degradation products (lowGDP), and with standard dialysis fluids (control).

Figure 2 — Hydration status (HS) in patients treated with fluids characterized by low concentration of glucose degradation products (lowGDP), and with standard dialysis fluids (control).

(Figure 3b). The type of dialysis fluid was a significant predictor of HS at the end of the study ($R^2 = 0.29$, $p = 0.03$), but it lost its predictive potential when adjusted for age, gender, and peritoneal transport.

DISCUSSION

High-glucose concentrations, as well as significant levels of GDPs, hyperosmolarity, acidic pH, and lactate buffer, are all recognized as deficiencies of standard PD fluids. At least some of these have been improved with the introduction of

Figure 3a — Extracellular volume (ECV) in patients treated with fluids characterized by low concentration of glucose degradation products (lowGDP), and with standard dialysis fluids (control).

Figure 3b — Intracellular volume (ICV) in patients treated with fluids characterized by low concentration of glucose degradation products (lowGDP), and with standard dialysis fluids (control).

biocompatible dialysis solutions. The biologic reasoning as well as numerous experimental studies seemed to support the increasing application of these fluids. In comparison with standard fluids, biocompatible fluids were shown to improve the viability of human peritoneal mesothelial cells *in vitro*, and to protect these cells from DNA damage (2), as well as to exert a beneficial impact on peripheral blood mononuclear cells functionality (3). Animal studies showed that the use of biocompatible fluids was associated with a less pronounced increase in vascular endothelial growth factor (VEGF) expression and vascular density, lower accumulation of advanced glycation end products (AGEs), and less submesothelial fibrosis, compared with conventional solutions (4,5). Similar findings were demonstrated in humans (6). Since the loss of peritoneal membrane function remains a major factor leading to treatment failure in PD, these results seemed very promising. Moreover, prospective randomized studies suggested improvements in RRF associated with biocompatible solutions (7–10). A recent systematic review of randomized controlled trials demonstrated that indeed, the biocompatible fluids preserved and improved RRF compared with conventional solutions (11). Since the loss of RRF is an acknowledged risk factor for mortality in PD subjects (12), these associations are believed to be of clinical importance. Indeed, some clinical observational studies suggested even survival benefits associated with the use of these novel fluids (13). However, along with these promising data, uncertainties started to arise that the slower decline in RRF might be due to a relative fluid overload in patients treated with biocompatible solutions (8). Our results seem to support this hypothesis. Hydration status, assessed with the use of bioimpedance spectroscopy, increased gradually in patients treated with low-GDP fluids and, at the end of the study, was significantly higher than in the control group. This was not associated with differences in RRF. Although we did not analyze glomerular filtration rate, the urine volume decreased similarly in both groups. This observation is in accordance with some other reports in which, similarly, the authors could not detect differences in RRF decline between patients treated with conventional vs biocompatible solutions (14,15). However, a recent meta-analysis revealed that the use of neutral-pH, low-GDP PD solutions was associated with larger urine volumes, although improved preservation of RRF was evident in studies with a follow-up longer than 12 months (16). This was not the case in our evaluation, despite the 2 years of observation time, maybe due to the small sample size, to the fact that the patients were prevalent PD subjects, with different dialysis vintages, or to some other, unrecognized factors.

The bioimpedance-assessed overhydration did not translate into any clinical features of excess water, such as body weight, the presence of edema, increase in blood pressure, or the use of antihypertensive medications. Similarly, although NTproBNP is known to correlate with changes in fluid volume (17), the concentration of NTproBNP remained fairly stable throughout the observation period and did not differ significantly between the groups. Finally, changes in HS were not paralleled by changes

in echocardiographic indices of overhydration. Nevertheless, the huge difference in HS between the 2 groups appears to be not only of statistical, but also of clinical significance. The bioimpedance spectroscopy has proved to be a technique with a potential to provide detailed clinically useful information about the hydration state of PD patients (18,19). In particular, it has been acknowledged that serial measurements, such as those undertaken in the current study, can identify changes in hydration earlier than routine clinical monitoring (18,20).

The most plausible cause of increased hydration in the low-GDP group is the decline in dialysis ultrafiltration, observed in these patients throughout the study. This observation is supported by the results of previous reports (21,22). The mechanisms leading to decreased ultrafiltration remain obscure. The possible explanation is the different effect of particular fluids on the peritoneal membrane. Conventional solutions with acidic pH and high concentration of GDPs are thought to induce a marked vasodilatation and recruitment of capillaries (7,23).

The major limitation of the present study is the relatively small sample size evaluated. This precluded randomization, and the patients were matched between the groups to achieve cohorts that were comparable in terms of baseline characteristics. The strengths include a thorough, multidimensional evaluation of HS parameters over a relatively long observation time.

In conclusion, dialysis with the use of low-GDP so-called biocompatible solutions was associated with a decline in peritoneal ultrafiltration rates paralleled by the increase in HS in prevalent PD patients. Additional studies are needed to assess the clinical importance of these findings.

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DISCLOSURES

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REFERENCES

1. Blake PG, Jain AK, Yohanna S. Biocompatible peritoneal dialysis solutions: many questions but few answers. *Kidney Int* 2013; 84(5):864–6.
2. Ha H, Yu MR, Choi HN, Cha MK, Kang HS, Kim MH, *et al.* Effects of conventional and new peritoneal dialysis solutions on human peritoneal mesothelial cell viability and proliferation. *Perit Dial Int* 2000; 20(Suppl 5):S10–8.
3. Sundaram S, Cendoroglo M, Cooker LA, Jaber BL, Faict D, Holmes CJ, *et al.* Effect of two-chambered bicarbonate lactate-buffered peritoneal dialysis fluids on peripheral blood mononuclear cell and polymorphonuclear cell function *in vitro*. *Am J Kidney Dis* 1997; 30(5):680–9.

4. Mortier S, Faict D, Schalkwijk CG, Lameire NH, De Vriese AS. Long-term exposure to new peritoneal dialysis solutions: effects on the peritoneal membrane. *Kidney Int* 2004; 66(3):1257–65.
5. Mortier S, Faict D, Lameire NH, De Vriese AS. Benefits of switching from a conventional to a low-GDP bicarbonate/lactate-buffered dialysis solution in a rat model. *Kidney Int* 2005; 67(4):1559–65.
6. Kawanishi K, Honda K, Tsukada M, Oda H, Nitta K. Neutral solution low in glucose degradation products is associated with less peritoneal fibrosis and vascular sclerosis in patients receiving peritoneal dialysis. *Perit Dial Int* 2013; 33(3):242–51.
7. Williams JD, Topley N, Craig KJ, Mackenzie RK, Pischetsrieder M, Lage C, et al. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (Balance) on the peritoneal membrane. *Kidney Int* 2004; 66(1):408–18.
8. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, et al. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. *J Am Soc Nephrol* 2012; 23(6):1097–107.
9. Kim SG, Kim S, Hwang YH, Kim K, Oh JE, Chung W, et al. Could solutions low in glucose degradation products preserve residual renal function in incident peritoneal dialysis patients? A 1-year multicenter prospective randomized controlled trial (Balnet Study). *Perit Dial Int* 2008; 28(Suppl 3):S117–22.
10. Lai KN, Lam MF, Leung JC, Chan LY, Lam CW, Chan IH, et al. A study of the clinical and biochemical profile of peritoneal dialysis fluid low in glucose degradation products. *Perit Dial Int* 2012; 32(3):280–91.
11. Seo EY, An SH, Cho JH, Suh HS, Park SH, Gwak H, et al. Effect of biocompatible peritoneal dialysis solution on residual renal function: a systematic review of randomized controlled trials. *Perit Dial Int* 2014; 34(7):724–31.
12. Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol* 2001; 12(10):2158–62.
13. Lee HY, Choi HY, Park HC, Seo BJ, Do JY, Yun SR, et al. Changing prescribing practice in CAPD patients in Korea: increased utilization of low GDP solutions improves patient outcome. *Nephrol Dial Transplant* 2006; 21(10):2893–9.
14. Szeto CC, Chow KM, Lam CW, Leung CB, Kwan BC, Chung KY, et al. Clinical biocompatibility of a neutral peritoneal dialysis solution with minimal glucose-degradation products—a 1-year randomized control trial. *Nephrol Dial Transplant* 2007; 22(2):552–9.
15. Fan SL, Pile T, Punzalan S, Raftery MJ, Yaqoob MM. Randomized controlled study of biocompatible peritoneal dialysis solutions: effect on residual renal function. *Kidney Int* 2008; 73(2):200–6.
16. Cho Y, Johnson DW, Badve SV, Craig JC, Strippoli GF, Wiggins KJ. The impact of neutral-pH peritoneal dialysates with reduced glucose degradation products on clinical outcomes in peritoneal dialysis patients. *Kidney Int* 2013; 84(5):969–79.
17. Davenport A. Changes in N-terminal pro-brain natriuretic peptide correlate with fluid volume changes assessed by bioimpedance in peritoneal dialysis patients. *Am J Nephrol* 2012; 36(4):371–6.
18. Woodrow G, Devine Y, Cullen M, Lindley E. Application of bioelectrical impedance to clinical assessment of body composition in peritoneal dialysis. *Perit Dial Int* 2007; 27(5):496–502.
19. Kwan BC, Szeto CC, Chow KM, Law MC, Cheng MS, Leung CB, et al. Bioimpedance spectroscopy for the detection of fluid overload in Chinese peritoneal dialysis patients. *Perit Dial Int* 2014; 34(4):409–16.
20. Woodrow G. Body composition analysis techniques in adult and pediatric patients: how reliable are they? How useful are they clinically? *Perit Dial Int* 2007; 27(Suppl 2):S245–9.
21. Kim S, Oh J, Chung W, Ahn C, Kim SG, Oh KH. Benefits of biocompatible PD fluid for preservation of residual renal function in incident CAPD patients: a 1-year study. *Nephrol Dial Transplant* 2009; 24(9):2899–908.
22. Fang W, Mullan R, Shah H, Mujais S, Bargman JM, Oreopoulos DG. Comparison between bicarbonate/lactate and standard lactate dialysis solution in peritoneal transport and ultrafiltration: a prospective, crossover single-dwell study. *Perit Dial Int* 2008; 28(1):35–43.
23. Mortier S, De Vriese AS, Van de Voorde J, Schaub TP, Passlick-Deetjen J, Lameire NH. Hemodynamic effects of peritoneal dialysis solutions on the rat peritoneal membrane: role of acidity, buffer choice, glucose concentration, and glucose degradation products. *J Am Soc Nephrol* 2002; 13(2):480–9.