RESEARCH ARTICLE

The Effect of Neutral Peritoneal Dialysis Solution with Low Glucose-Degradation-Product on the Fluid Status and Body Composition – A Randomized Control Trial

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Abstract

Background
Previous studies report conflicting results on the benefit of peritoneal dialysis (PD) patients treated with low glucose degradation product (GDP) solution. The effects of low GDP solution on body fluid status and arterial pulse wave velocity (PWV) have not been studied.

Methods
We randomly assigned 68 incident PD patients to low GDP (Intervention Group) or conventional solutions (Control Group); 4 dropped off before they received the assigned treatment. Patients were followed for 52 weeks for changes in ultrafiltration, residual renal function, body fluid status and arterial PWV.

Result
After 52 weeks, Intervention Group had higher overhydration (3.1 ± 2.6 vs 1.9 ± 2.2 L, p = 0.045) and extracellular water volume (17.7 ± 3.9 vs 15.8 ± 3.1 L, p = 0.034) than Control Group. There was no significant difference in PWV between groups. There was no significant difference in residual renal function between the Groups. Intervention Group had lower ultrafiltration volume than Control Group at 4 weeks (0.45 ± 0.61 vs 0.90 ± 0.79 L/day, p = 0.013), but the difference became insignificant at later time points. Intervention Group had lower serum CRP levels than Control Group (4.17 ± 0.77 vs 4.91 ± 0.95 mg/dL, p < 0.0001).

Conclusion
Incident PD patients treated with low GDP solution have less severe systemic inflammation but trends of less ultrafiltration, and more fluid accumulation. However, the effects on ultrafiltration and fluid accumulation disappear with time. The long term effect of low GDP solution requires further study.
Trial Registration
ClinicalTrials.gov NCT00966615

Introduction

Long term peritoneal dialysis (PD) by bio-incompatible solution has been proposed to be the cause of progressive loss of peritoneal permeability [1,2]. Amongst the ingredients in conventional PD solution, its acidic pH and the presence of glucose-degradation-product (GDP) are probably the major factors resulting in bio-incompatibility [3,4]. In recent years, a double-chamber bag Stay-Safe® Balance system (Fresenius Medical Care, Bad Homburg, Germany) was developed. The ready-to-use solution has a physiological pH and a highly reduced amount of GDP [5].

A number of early studies suggested beneficial effects of the lactate-based pH-neutral solution on several components of the peritoneum [6–8]. The clinical benefit of this neutral low GDP solution, however, remains unclear. In a European multicenter prospective crossover trial that compared conventional solution with the new neutral solution [9], patients treated with the new solution had an improved profile of dialysate mesothelial markers. In our previous study, the use of neutral pH, low GDP solution resulted in a superior profile of PD effluent mesothelial cell marker and a lower degree of systemic inflammation as compared to conventional PD solution [10]. Other studies have reported variable and sometimes conflicting effects of low GDP solutions on ultrafiltration volume, urine output, decline of residual renal function, and peritonitis rate [9–17]. More importantly, there are no published data on the effect of low GDP solution on the overall body fluid status or arterial stiffness of PD patients. In the present study, we compare a double-chamber bag Stay-Safe® Balance system and the conventional glucose-based solution in terms of nutritional status, arterial stiffness, and body composition and fluid status.

Patients and Methods

The study was approved by our local clinical research ethics committee (Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee). The study procedure was performed according to the Declaration of Helsinki and registered at ClinicalTrials.gov (ID NCT00966615).

Overall arrangement

We recruited new adult continuous ambulatory peritoneal dialysis (CAPD) patients from February 2011 to July 2013. After written informed consent, they were randomized by a standard randomization table, which was kept by a third party, to receive the Balance System (Intervention Group) or a disconnect system with glucose-based dialysis solution (Stay-Safe®, Fresenius Medical Care, Germany) (Control Group). The biochemical composition of the two solutions is summarized in S1 Table. We excluded patients who were unlikely to survive, planned to have elective living-related kidney transplant, or transfer to other renal center within 6 months. Training for CAPD exchange was performed according to our routine clinical practice. All patients received home-based CAPD treatment after training was completed. The use of Stay-Safe® solution has been the usual care of around half of our PD population in the past 10 years.
Clinical follow up

Patients were followed at 0, 4, 8, 16, 24, 32, 40 and 52 weeks. Except for the dialysis solution preparation, the clinical management was identical for the two groups. During each follow up visit, we measured body weight, blood pressure, presence of edema, and compliance to dialysis exchange by direct questioning. Hemoglobin level, serum electrolytes, urea and creatinine were checked upon each clinic visit. Dialysis regimen was adjusted according to clinical assessment of fluid status, urine output, and record of ultrafiltration by the patient. A glucose polymer solution was not used because of the difference in connection tubing. Physicians were blinded from the result of bioimpedance spectroscopy or arterial pulse wave velocity throughout the study. The use of anti-hypertensive drug was quantified by the numbers and defined daily doses of antihypertensive drugs (one defined daily dose is the average maintenance dose per day for adults) [18]. Hypertonic cycle was defined as any PD exchange with dextrose concentration higher than 1.5%, which was generally used when the patient had inadequate ultrafiltration or clinical evidence of fluid overload.

Bioimpedance Spectroscopy

Body composition was assessed at 4, 24 and 52 weeks by bioimpedance spectroscopy (Body Composition Monitor, Fresenius Medical Care, Germany) with PD solution instilled. The method of bioimpedance spectroscopy has been described previously [19]. We computed the following parameters from this test: total body water, intracellular water, and extracellular water, lean tissue mass (LTM), adipose tissue mass (ATM), and volume of over hydration.

Arterial Pulse Wave Velocity Study

Pulse wave velocity (PWV), an index of aortic stiffness, was measured at 4 and 52 weeks using an automatic computerized recorder and the results are analyzed using the Complior SP pro (Artech Medical, France). The method of PWV measurement has been described previously [20].

Assessment of peritoneal transport

Peritoneal transport was assessed at 4 and 52 weeks. We used the standard PET as described by Twardowski [21]. Dialysate-to-plasma ratios of creatinine (D/P) at 4 hours was calculated after correction of glucose interference [22]. Mass transfer area coefficients of creatinine (MTAC) normalized for body surface area (BSA) was calculated by the formula described by Krediet [23].

Dialysis adequacy and nutritional status

Dialysis adequacy was assessed at 4, 24 and 52 weeks by 24-hour dialysate and urine collections. Total Kt/V, a measurement of body urea clearance provided by dialysis and the residual kidney function, was determined by standard methods. Residual glomerular filtration rate (GFR) was calculated as the average of 24-hour urinary urea and creatinine clearance [24]. We also computed the normalized protein nitrogen appearance (NPNA) by the Bergstrom’s formula [25], and fat-free edema-free body mass (FEBM) by creatinine kinetics according to the formula of Forbes and Bruining [26].

In addition to FEBM and NPNA, nutritional status was represented by Subjective global assessment (SGA) score [27], the comprehensive malnutrition-inflammation score (MIS) [28], serum albumin and C-reactive protein (CRP) at 4, 24 and 52 weeks. SGA was measured in a 7-point scale; a higher score means better nutrition [27]. MIS a combination score of 10 items,
with a total score of 30; a higher score means worse nutrition [28]. Serum C-reactive protein (CRP) was measured by the Tina-quant CRP (Latex) ultra-sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany).

Clinical Outcome

All patients were followed for 12 months. The primary outcome measures are the change in body composition and arterial pulse wave velocity. The latter was chosen as a primary outcome measure because our previous study showed that asymptomatic fluid overload in PD patients may result in worsening of arterial PWV [19]. Secondary outcomes include nutritional and adequacy indices, peritoneal transport characteristics, residual renal function, peritonitis-free survival, hospitalization, and patient survival and technique survival. Technique failure is defined as transfer to other modes of renal replacement therapy.

Sample size

The sample size was estimated by the Power Analysis and Sample Size for Windows software (PASS 2000, NCSS, Kaysville, Utah), calculated on the base of simple comparison. Based on our previous studies [20,29], aortic PWV is expected to be 10.2 ± 1.6 m/sec. We assumed a difference of 1 m/sec in the PWV to be clinically meaningful. Group sizes of 45 achieve 80% power to detect such a difference of PWV, with a significance level (alpha) of 0.05. Allowing for 10% drop out rate, the study was estimated to require 100 patients in total.

Statistical Analysis

Statistical analysis is performed by SPSS for Windows software version 18.0 (SPSS Inc., Chicago, IL). All data are expressed in mean ± standard deviation unless otherwise specified. Since all the primary outcome measures were serial biochemical and laboratory parameters, which were not available for patients who did not receive the assigned treatment, only the result of per protocol analysis is presented. Parameters between groups are compared by Chi-square test, Student’s t test, or Mann-Whitney U test as appropriate. Serial data are compared by paired Student’s t test. Multivariate analysis was not performed to adjust for confounding factors because of the small number of patients. Peritonitis-free survival between groups were calculated by Kaplan Meier survival plot and compared by the log rank test. A P value of less than 0.05 is considered statistically significant; Bonferroni method is used to correct for multiple comparisons. All probabilities are two-tailed.

Results

During the recruitment period, we obtained consent from 68 patients, but 4 were excluded before treatment was started. Fig 1 depicts the Consort flow diagram that summarizes the trial profile. The baseline clinical characteristics of the 64 patients who received their assigned treatment are summarized in Table 1. In essence, the Intervention Group had more diabetic patients (64.5% vs 33.3%), tend to be older (62.9 vs 57.7 years), and had higher Charlson’s scores than the Control Group.

Body composition and fluid status

Blood pressure, dialysis regimen, use of diuretic agents, and peritoneal transport characteristics are compared in Table 2. Both at 4 and 52 weeks, the Intervention Group had a trend of using more hypertonic cycle and diuretic agents than the Control Group, although none of the difference was significant. The total glucose load during the study period was marginally higher in
the Intervention than Control Group (38.8 ± 12.2 vs 33.8 ± 7.5 kg, p = 0.06). At 4 weeks, the Intervention Group had higher D/P creatinine at 4 hours and MTAC creatinine than the Control Group (Table 2), but the difference became insignificant by 52 weeks.

The body composition and fluid status of the two groups are compared in Fig 2. In essence, there was no difference in the baseline body composition and fluid status between the two groups. After 24 weeks, the Intervention Group had higher overhydration (4.3 ± 2.9 vs 2.5 ± 2.2 L, p = 0.007), extracellular water volume (18.3 ± 3.8 vs 15.7 ± 3.9 L, p = 0.009), E:I ratio (1.04 ± 0.16 vs 0.92 ± 0.14, p = 0.004), total body water (36.0 ± 6.3 vs 32.8 ± 7.5 L, p = 0.07), and body weight (62.9 ± 12.1 vs 59.6 ± 10.1 kg, p = 0.055), although the results of total body water and body weight are not significant. These differences persisted but became less marked by 52 weeks. When diabetic and non-diabetic patients were separately analyzed, there was no difference in overhydration or E:I ratio between Intervention and Control Group at any time point (Table 2). There was no significant difference in lean tissue mass (LTM) or adipose tissue mass (ATM) between the two Groups throughout the study period. ATM increased modestly in both group, while LTM remained static, during follow up.

Arterial pulse wave velocity

The arterial pulse wave velocity of the two groups are compared and summarized in Fig 3. Both carotid-femoral and carotid-radial PWV were similar between the Intervention and
Control Groups at 4 weeks. After 52 weeks of PD, carotid-femoral PWV had a modest but significant increase in the Intervention Group (12.1 ± 2.8 to 13.2 ± 3.1 m/sec, paired t-test, p = 0.001), while it remained static in the Control Group. Carotid-radial PWV remained static in both Groups. At 52 weeks, the Intervention Group had slightly higher carotid-femoral PWV than the Control Group (13.2 ± 3.1 vs 11.8 ± 2.0 m/sec, p = 0.04), but the carotid-radial PWV were similar. When diabetic and non-diabetic patients were separately analyzed, there was no difference in PWV between the two groups at any time point (Table 2).

Residual renal function, inflammation, and nutritional status

Fluid removal, dialysis adequacy, and residual renal function of the two groups during the study period are compared in Fig 4. By univariate analysis, the Intervention Group had a lower ultrafiltration volume than the Control Group 4 weeks after PD (0.45 ± .0.61 vs 0.90 ± 0.79 L/day, p = 0.013), but the difference became insignificant at later time points. In contrast, there was a progressive decline in urine output, residual GFR, and total Kt/V, together with a corresponding increase in ultrafiltration volume in both Groups during the study period. At 52 weeks, the Intervention Group had a trend of higher urine output (0.81 ± 0.66 vs 0.58 ± 0.52 L/day, p = 0.16) and residual GFR (2.80 ± 2.09 vs 1.78 ± 1.56 ml/min/1.73m², p = 0.07) than the Control Group, but the difference was not significant. After one year, 5 patients from each group progressed to anuria.

During the first year of PD, the Control Group had a significant increase in serum CRP level, while the Intervention Group also had an insignificant trend of rising CRP (Fig 5). At 52 weeks, the Intervention Group had a significantly lower serum CRP level than the Control Group (4.17 ± 0.77 vs 4.91 ± 0.95 mg/DL, p < 0.0001). There was also a trend of progressive decline in SGA score and a corresponding increase in MIS in both Groups during the study (Table 3), but the change was not statistically significant. There was no significant difference in other nutritional indices between the two Groups (Table 3).

### Table 1. Baseline characteristics of the patients.

|                        | Intervention Group | Control Group |
|------------------------|--------------------|--------------|
| No. of patient         | 31                 | 33           |
| Sex (M:F)              | 17:14              | 13:20        |
| Age (years)            | 62.9 ± 12.1        | 57.7 ± 9.9   |
| Body height (cm)       | 162.4 ± 8.8        | 160.9 ± 8.3  |
| Body mass index (kg/m²)| 24.4 ± 3.1         | 23.0 ± 3.1   |
| Diagnosis, no. of cases (%) |                  |              |
| Glomerulonephritis     | 6 (19.4%)          | 12 (36.4%)   |
| Diabetic nephropathy   | 18 (58.1%)         | 9 (27.3%)    |
| Hypertensive nephrosclerosis | 6 (19.4%)        | 4 (12.1%)    |
| Polycystic kidney      | 0                  | 1 (3.0%)     |
| Obstruction            | 1 (3.2%)           | 4 (12.1%)    |
| Others / unknown       | 0                  | 3 (9.1%)     |
| Major comorbidity, no. of cases (%) |        |              |
| Diabetes               | 20 (64.5%)         | 11 (33.3%)   |
| Coronary heart disease | 4 (12.9%)          | 4 (12.1%)    |
| Cerebrovascular disease| 7 (22.6%)          | 5 (15.2%)    |
| Charlson’s Index score | 6.2 ± 2.1          | 5.1 ± 2.2    |

Data are presented as mean ± standard deviation.

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Peritonitis, hospitalization, survival, and adverse reactions

Peritonitis and hospital admission of the two groups during the study period are compared in Table 4. The peritonitis-free survival at 52 weeks was 74.2% and 75.8% for in the Intervention and Control Groups, respectively (p = 0.9) (S1 Fig). During the study period, one patient from each Group died, and none had kidney transplant after CAPD was started or transfer to long-term hemodialysis. Analysis of patient or technique survival is not performed due to the small number of event. There was no adverse reactions reported in either study group.

Discussion

In this randomized control study, we found that new PD patients treated with low GDP solution had more fluid accumulation, less ultrafiltration from PD, but more urine output than
patients treated with conventional PD solutions. As compared to the control group, patients receiving the low GDP solution also had less severe systemic inflammation but higher carotid-femoral arterial PWV after one year of PD.

Although there are a number of randomized control trials on the possible benefit low GDP solutions [30], our present study is the first one that examines body fluid status in detail. Three previous studies reported no significant difference in body weight between patients treated with low GDP solutions and those with conventional ones at 12 and 24 months [12–14]. Our result indicates that after 6 months of PD, although low GDP solution has no substantial effect on the overall body weight or blood pressure, these patients tend to have more overhydration, extra-cellular water (ECW) volume, and extracellular-to-intracellular fluid (E:I) ratio than patients treated with conventional solutions. However, it is important to note the effect of low GDP solution on overhydration and ECW volume became less marked at 12 months, probably because of the loss of residual renal function in the Control Group.

The cause of excessive fluid accumulation in the Intervention Group is unclear. In spite of randomization, there were more diabetic patients in the Intervention Group, which may potentially affect the result. A previous report shows that diabetic patients have substantial alterations of the peritoneal structure [31], which may explain the higher D/P creatinine, worse ultrafiltration, and more fluid overload in our Intervention Group. There were also slightly
more men in the Intervention Group, which might also contribute to more fluid overload in this group. In the present study, we did not document the dietary intake, and we cannot exclude the possibility that the Intervention Group had a better appetite and more salt and water intake than the Control Group. On the other hand, the excessive fluid accumulation could be the result of less fluid removal by ultrafiltration (see Fig 4). Several previous studies found a lower ultrafiltration volume with the use of low GDP solutions [9,14,15], although others showed no significant effect [10,13,16]. In the balANZ Trial, patients in the biocompatible group had significantly lower ultrafiltration at 3 and 6 months but not later time points [12,32]. Taken together, available data suggest a modest negative effect of low GDP solution on peritoneal ultrafiltration. However, the effect seems to disappear with time, and the clinical relevance is uncertain.

We found no difference in residual GFR decline, urine output, or progression to anuria between the two groups. Although several studies observed better preservation of residual renal function by low GDP solutions [14–16], three major randomized control trials found that low GDP solution has no effect in slowing the rate of GFR decline [12,13,17]. In our study, the use of diuretic agents was similar between the Groups, suggesting that the higher urine output amongst patients treated with low GDP solution is not related to diuretic therapy.
We found conflicting changes in arterial PWV and serum CRP levels. After 12 months of PD, patients treated with low GDP solution had more marked increase in carotid-femoral PWV, indicating progressive arterial stiffening, but a lower serum CRP level, suggesting an amelioration of the systemic inflammatory state. Notably, the effect of low GDP solution on arterial stiffness has not been examined in previous studies. The rapid progression of arterial stiffness in the Intervention Group is probably explained by the imbalance in baseline characteristics, because the difference disappears after adjusting for confounding factors. However, the progression of arterial stiffness may partly represent the chronic effect of overhydration, supporting the notion that long-standing mild fluid overload has clinical consequence, which has been reported by several groups previously [19,33]. On the other hand, the effect of low GDP solution on systemic inflammation remains uncertain. While two previous studies showed that the use of low GDP solution resulted in lower serum CRP levels [10,17], others found no difference [13,14,16].

Although our results do not suggest a favorable effect of low GDP solution on body fluid status or arterial pulse wave velocity, there could have been bias in our study because, despite
randomization, the proportion of diabetic patient is significantly higher in the Intervention Group and this group of patients tend to be older. Although the result remains similar when diabetic and non-diabetic patients are analyzed separately, the number of patient is small with subgroup analysis and there could be statistical error.

There are other limitations of our study. First, the sample size is small and we do not have sufficient power to determine a small but clinically important difference in residual renal function, peritonitis or hospitalization rate. We encountered unexpected difficulties during recruitment, and we could only recruit 68 out of 100 patients as originally planned. However, our sample size was estimated by the difference in PWV, of which we do find a difference between the Groups. Furthermore, the duration of our study may not be sufficient. As noticed in our

Fig 5. Serum C-reactive protein (CRP) during the study period. Error bars denote standard deviations; P values denote the comparison between the Intervention and Control Groups by the Student’s t test. (Grey box, Intervention Group; White box, Control Group).
study as well as the balANZ trial [12], the initial undesirable effects of low GDP solution on ultrafiltration, peritoneal transport, and body fluid status diminish with time. It remains unknown whether prolonged use of low GDP solution would help to preserve peritoneal function. Long term study is necessary to test this hypothesis.

Secondly, we used multiple-frequency bioimpedance spectroscopy for the measurement of body composition and fluid status. Although the method has a good overall agreement to the gold-standard isotope dilution techniques, the intra-individual variability is considerable [34]. Unfortunately, we do not have baseline fluid status before dialysis was started, or data on cardiac function. Similarly, we do not have data on peritoneal transport before dialysis because peritoneal transport characteristics change significantly within the first month of PD [35] and determination of “baseline” peritoneal transport status was not possible.

In summary, incident PD patients treated with low GDP solution have less severe systemic inflammation but trends of less ultrafiltration, and more fluid accumulation. However, the effects on ultrafiltration and fluid accumulation disappear with time. The long term effect of low GDP solution requires further study.

Table 3. Nutritional indices during the study period.

|                      | Intervention Group | Control Group |          |
|----------------------|--------------------|---------------|----------|
|                      | 4 weeks            | 24 weeks      | 52 weeks |
| Hemoglobin (g/dL)    | 9.54 ± 1.77        | 9.87 ± 1.47   | 9.66 ± 1.65 |
| Serum albumin (g/L)  | 33.9 ± 4.3         | 34.7 ± 3.8    | 35.2 ± 3.1 |
| NPNA (g/kg/day)      | 1.08 ± 0.21        | 1.18 ± 0.23   | 1.15 ± 0.17 |
| FEBM (%)             | 38.5 ± 8.3         | 43.6 ± 10.8   | 46.7 ± 10.7 |
| MIS                  | 8.0 ± 3.4          | 10.1 ± 4.2    | 11.1 ± 3.5  |
| SGA score            | 5.5 ± 0.8          | 5.1 ± 0.9     | 4.9 ± 0.8   |

NPNA, normalized protein nitrogen appearance; FEBM, fat-free edema-free body mass; MIS, malnutrition inflammation score; SGA, subjective global assessment. Data are presented as mean ± standard deviation.

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Table 4. Peritonitis and hospital admission during the study period.

|                      | Intervention Group | Control Group | P value |
|----------------------|--------------------|---------------|---------|
| No. of patient       | 31                 | 33            |         |
| Peritonitis          |                    |               |         |
| no. of peritonitis episodes | 9       | 11            | p = 0.8 |
| no. of patients being peritonitis-free | 23    | 25            | p = 0.9 |
| Hospital admission   |                    |               |         |
| all cause            |                    |               |         |
| no. of hospital admission | 53    | 35            | p = 0.4 |
| duration of hospitalization (days) | 315    | 249           | p = 0.3 |
| admission for CVD    |                    |               |         |
| no. of hospital admission | 14    | 7             | p = 0.4 |
| duration of hospitalization (days) | 80    | 78            | p = 0.4 |
| Death, no. of patient (cause) | 1 (CVD) | 1 (infection) |         |

CVD, cardiovascular disease.

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Supporting Information

S1 CONSORT Checklist. CONSORT checklist.
(DOC)

S1 Fig. Kaplan-Meier plot of peritonitis-free survival.
(TIF)

S1 File. Participant-level data.
(XLSX)

S1 Protocol. Trial protocol.
(DOC)

S1 Table. Biochemical composition of the peritoneal dialysis solutions.
(DOCX)

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Author Contributions

Conceived and designed the experiments: CCS PKTL. Performed the experiments: BCHK KMC PMSC VWKK ASMC MCL CBL. Analyzed the data: CCS PMSC. Contributed reagents/materials/analysis tools: PKTL. Wrote the paper: CCS PKTL.

References

1. Davies SJ, Bryan J, Phillips L, Russell GI. Longitudinal changes in peritoneal kinetics: the effects of peritoneal dialysis and peritonitis. Nephrol Dial Transplant 1996; 11: 498–506. PMID: 8671921
2. Breborowicz A, Oreopoulos DG. Biocompatibility of peritoneal dialysis solutions. Am J Kidney Dis 1996; 27: 738–743. PMID: 8629638
3. Liberek T, Topley N, Jorres A, Petersen MM, Coles GA, Gahl GM, et al. Peritoneal dialysis fluid inhibition of polymorphonuclear leucocyte respiratory burst activation is related to the lowering of intracellular pH. Nephrol 1993; 65: 260–265.
4. Cappelli G, Bandiani G, Cancarini GC, Feriani M, Dell’Aquila R, Saffioti S, et al. Low concentrations of glucose degradation products in peritoneal dialysis fluids and their impact on biocompatibility parameters: prospective cross-over study with a three-compartment bag. Adv Perit Dial 1999; 15: 238–242. PMID: 10682110
5. van Biesen W, Kirchgessner J, Schilling H, Lage C, Lambert MC, Passlick-Deetjen J. Stay-Safe<sup>®</sup>, a new PCV-free system for PD: results of the multicenter trial. Perit Dial Int 1999; 19(Suppl 1): S43.
6. Lage C, Pischetsrieder M, Aufricht C, Jorres A, Schilling H, Passlick-Deetjen J. First in vitro and in vivo experiences with Stay-Safe Balance, a pH-neutral solution in a dual-chambered bag. Perit Dial Int: 2000; 20 (Suppl 5): S28–32. PMID: 11229609
7. Ascher DM, Pauli-Magnus C, Kirchgessner J, Kuhimann U, Mettang T. A new lactate-based, plasticizer-free, neutral peritoneal dialysis fluid provided in a two-compartment system: effect on peripheral leukocyte function. Nephron: 2000; 86: 62–69. PMID: 10971155
8. Passlick-Deetjen J, Pischetsrieder M, Witowski J, Bender TO, Jorres A, et al. In vitro superiority of dual-chambered peritoneal dialysis solution with possible clinical benefits. Perit Dial Int. 2001; 21 (Suppl 3): S96–101. PMID: 11887872
9. 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: 408–418. PMID:15200450

10. 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 one-year randomized control trial. Nephrol Dial Transplant 2007; 22: 552–559. PMID:17005526

11. Schmitt CP, Haraldsson B, Doetschmann R, Zimmering M, Greiner C, Boswald M, et al. Effects of pH-neutral, bicarbonate-buffered dialysis fluid on peritoneal transport kinetics in children. Kidney Int 2002; 61: 1527–1536. PMID:11918761

12. 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: 1097–1107. doi: 10.1681/ASN.2011121201 PMID: 22440906

13. 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: 200–206. PMID:17914351

14. Kim S, Oh J, Kim S, Chung W, Ahn C, Kim SG, et al. Benefits of biocompatible PD fluid for preservation of residual renal function in incident CAPD patients: a 1-year study. Nephrol Dial Transplant 2009; 24: 2899–2908. doi: 10.1093/ndt/gfp054 PMID: 19258384

15. Montenegro J, Saracho RM, Martinez IM, Muñoz RI, Ocharan JJ, Valladares E. Long-term clinical experience with pure bicarbonate peritoneal dialysis solutions. Perit Dial Int 2006; 26: 94. PMID:16538881

16. Haag-Weber M, Krämer R, Haake R, Islam MS, Prischl F, Haug U, et al. Low-GDP fluid (Gambrosol trio) attenuates decline of residual renal function in PD patients: a prospective randomized study. Nephrol Dial Transplant 2010; 25: 2288–2296. doi: 10.1093/ndt/gfq087 PMID: 20179284

17. Choi HY, Kim DK, Lee TH, Moon SJ, Han SH, Lee JE, et al. The clinical usefulness of peritoneal dialysis solutions with neutral pH and low glucose degradation product concentration: an open randomized prospective study. Perit Dial Int 2008; 28: 174–182. PMID:18332454

18. WHO. Main principles for the establishment of Defined Daily Doses. In: Guidelines for ATC classification and DDD assignment. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology, 1995: 22–31.

19. Kwan BC, Szeto CC, Chow KM, Law MC, Cheng MS, Leung CB, et al. Biomeasurement spectroscopy for the detection of fluid overload in Chinese peritoneal dialysis patients. Perit Dial Int 2014; 34: 409–416. doi: 10.3747/pdi.2013.00066 PMID: 24385329

20. Li PK, Cheng YL, Leung CB, Szeto CC, Chow KM, Kwan BC, et al. Effect of membrane permeability on inflammation and arterial stiffness: a randomized trial. Clin J Am Soc Nephrol 2010; 5: 652–658 doi: 10.2215/CJN.05620809 PMID: 20203165

21. Twardowski ZJ, Nolph KD, Prowant B, Ryan L, Moore H, Nielsen MP. Peritoneal equilibration test. Perit Dial Bull 1987; 7: 138–147.

22. Mak TW, Cheung CK, Cheung CM, Leung CB, Lam CW, Lai KN. Interference of creatinine measurement in CAPD fluid was dependent on glucose and creatinine concentrations. Nephrol Dial Transplant 1997; 12: 184–186. PMID:9077796

23. Krediet RT, Boeschoten EW, Zuyderhoudt FMJ, Strackee J, Arisz L. Simple assessment of the efficacy of peritoneal transport in continuous ambulatory peritoneal dialysis patients. Blood Purification 1986; 4: 194–203. PMID: 3790265

24. Van Olden RW, Krediet RT, Struijk DG, Arisz L. Measurement of residual renal function in patients treated with continuous peritoneal dialysis. J Am Soc Nephrol 1996; 7: 745–748. PMID: 8738810

25. Bergström J, Heimbürger O, Lindholm B. Calculation of the protein equivalent of total nitrogen appearance from urea appearance. Which formulas should be used? Perit Dial Int 1998; 18: 467–473. PMID: 9846623

26. Forbes GB, Bruining GJ. Urinary creatinine excretion and lean body mass. Am J Clin Nutr 1976; 29: 1359–1366. PMID:998546

27. Enia G, Sicus C, Alati G, Zoccali C. Subjective global assessment of nutrition in dialysis patients. Nephrol Dial Transplant 1993; 8: 1094–1098. PMID:8272222

28. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis 2001; 38: 1251–1263. PMID:11728958

29. Szeto CC, Kwan BC, Chow KM, Leung CB, Law MC, Li PK. Prognostic value of arterial pulse wave velocity in peritoneal dialysis patients. Am J Nephrol 2012; 35: 127–133. doi: 10.1159/000335580 PMID: 22236995
30. 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: 969–979. doi: 10.1038/ki.2013.190 PMID: 23698236

31. Contreras-Velázquez JC, Soto V, Jaramillo-Rodríguez Y, Samaniego-Ríos LI, Quiñones-Pérez V, Avila M, et al. Clinical outcomes and peritoneal histology in patients starting peritoneal dialysis are related to diabetic status and serum albumin levels. Kidney Int Suppl 2008; 108: S34–41. doi: 10.1038/sj.ki.5002599 PMID: 18379545

32. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, et al. The effect of low glucose degradation product, neutral pH versus standard peritoneal dialysis solutions on peritoneal membrane function: the balANZ trial. Nephrol Dial Transplant 2012; 27: 4445–4453. doi: 10.1093/ndt/gfs314 PMID: 22859794

33. Kocyigit I, Sipahioglu MH, Orsceilk O, Unal A, Celik A, Abbas SR, et al. The association between arterial stiffness and fluid status in peritoneal dialysis patients. Perit Dial Int 2014; 34: 781–790. doi: 10.3747/pdi.2013.00057 PMID: 24385328

34. Davies SJ, Davenport A. The role of bioimpedance and biomarkers in helping to aid clinical decision-making of volume assessments in dialysis patients. Kidney Int 2014; 86: 489–496. doi: 10.1038/ki.2014.207 PMID: 24918155

35. Johnson DW, Mudge DW, Blizzard S, Arndt M, O’Shea A, Watt R, et al. A comparison of peritoneal equilibration tests performed 1 and 4 weeks after PD commencement. Perit Dial Int 2004; 24: 460–465. PMID: 15490986