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Influence of peritoneal dialysis solution biocompatibility on long-term survival of patients on continuous ambulatory peritoneal dialysis and the technique itself

Uticaj biokompatibilnosti rastvora za peritoneumsku dijalizu na višegodišnje preživljavanje bolesnika na kontinuiranoj ambulantnoj peritoneumskoj dijalizi i same metode lečenja

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Abstract

Background/Aim. Morbidity and mortality of continous ambulatory peritoneal dialysis (CAPD) patients is still very high. The aim of the study was to evaluate the effects of peritoneal dialysis (PD) solutions (standard *vs* biocompatible) on long-term patients' and the techique survival. **Methods.** A total of 42 stable patients on CAPD participated in this cross-sectional study. They were prospectively followed-up during the twelve years. Patients with severe anemia (Hb < 10 g/L) and malignant disease ware excluded. Twenty one (50%) patients were treated with the standard PD solutions (CAPDP-1) while the other 21 (50%) were treated with biocompatible PD solutions [(lower level of glucose degradation products, lower concentration of Ca^{2+} and neutral pH (CAPDP-2)]. All patients were analyzed for a presence of vascular calcification, nutrition status, and parameters of inflammation after 2.5 ± 0.6 years of starting CAPD, and these variables considered in the analysis as risk factors. **Results.** The patients from the group CAPDP-2 compared to those from the group CAPDP-1 had lower level of high-sensitivity C-reactive protein (hs-CRP) ($p = 0.003$), and better nutritional status as confirmed by the mid-arm circumference ($p = 0.015$), and mid-arm muscle circumference ($p = 0.002$) and subjective global assessment ($p = 0.000$). Also, they had lower vascular calcifications as confirmed by intima media thickness (IMT) ($p = 0.003$), degree of carotid narrowing ($p = 0.001$) and calcified plaques of common carotid arteries (CCA) ($p = 0.008$). Kaplan-Meier analysis confirmed better survival of patients from the group CAPDP-2 than those from the group CAPDP-1 (1-, 5-, and 10-year patients survival rate was: 100%, 61.9% and 14.3% for the group CAPDP-1, and 100%, 85.7%, and 52.4% for the group CAPDP-2, respectively; $p = 0.0345$). The 1-, 5-, and 10-year technique survival rate was: 100%, 71.4%, and 38.1% for the group CAPDP-1, and 100%, 85.7%, and 76.2% for the group CAPDP-2, respectively; ($p = 0.0719$). Duration of dialysis, serum triglyceride and cardiovascular score (quantitative scoring system consisting of: ejection fraction (EF) of left ventricle < 50%; IMT > 1 mm; carotid narrowing degree > 50%, presence of carotid plaques in both common carotide, ischaemic heart disease, cerebrovascular event and peripheral vascular disease with or without amputation) were independent predictors of overall patient survival. Duration of dialysis was only independent predictor of overall technique survival. **Conclusion.** Although patients treated with biocompatible solutions showed significantly better survival, the role of biocompatibility of CAPD solutions in patients and technique survival have to be confirmed. Namely, multivariate analysis confirmed that duration of dialysis, serum triglyceride and cardiovascular score significantly predicted overall CAPD patients survival, while only duration of dialysis was found to be independent predictor of overall techique survival.

Key words:
peritoneal dialysis, continuous ambulatory; survival analysis; dialysis solutions; morbidity; mortality; risk factors.

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Apstrakt

Uvod/Cilj. Morbiditet i mortalitet bolesnika na kontinuiranoj ambulantnoj peritoneumskoj dijalizi (KAPD) i dalje je neprihvatljivo visok. Cilj rada bio je da se proceni uticaj vrste dijaliznih rasvora (bioinkompatibilni *vs* biokompatibilni) na višegodišnje preživljavanje bolesnika i same tehnike KAPD. **Metode.** Ovom studijom preseka sa delimično prospektivnim praćenjem ishoda lečenja obuhvaćeno je ukupno 42 nasumice izabrana, stabilna bolesnika (26 muškaraca i 16 žena) lečena primenom metode KAPD tokom poslednjih 12 godina. Isključeni su bolesnici sa teškom anemijom (Hb <10 g/L) i malignom bolešću. Pri tome, 21 (50%) bolesnika kontinuirano je lečeno bioinkompatibilnim rastvorom za KAPD (kiseli standardni rastvor – ANDY-disc; grupa KAPDB-1), dok je preostalih 21 bolesnik sve vreme bilo na biokompatibilnijem rastvoru za KAPD (neutralni rastvor sa znatno manjom koncentracijom degradacionih produkata glukoze, 1.25 mmol/L Ca i 40 mmol/L laktata – Gambrosol Trio; grupa KAPDB-2). Svim bolesnicima određeni su odabrani parametri hronične inflamacije, malnutricije i ateroskleroze zajedno sa transportnim karakteristikama peritoneumske membrane i rezidualnom bubrežnom funkcijom nakon 2,5 ± 0,6 god od započinjanja KAPD. Svi dobijeni rezultati analizirani su kao potencijalni faktori rizika. **Rezultati.** Grupa KAPDB-2 u odnosu na KAPDB-1 imala je statistički značajno niže vrednosti serumskog hs-CRP (p = 0,003) i bolje parametre nutritivnog statusa izražene kroz obim nadlaktice (p = 0,015), obim mišića nadlaktice (p = 0,002) i subjektivnu globalnu procenu (p = 0,000) kao i u manjoj meri prisutnu aterosklerozu potvrđeno debljinom intimomedijalnog kompleksa (IMT) (p = 0,003), stepenom suženja karotida (p = 0,001) i prisustvom kalcifikovanih ateromatoznih plakova na karotidnim arterijama (p = 0,008). Kaplan-Meier-ova kriva preživljavanja potvrdila je značajno duže preživljavanje bolesnika u grupi KAPD-2 u odnosu na KAPDB-1 (1-, 5-, i 10-godišnje preživljavanje bolesnika iznosilo je redom: 100%, 61.9% i 14.3% u KAPDB-1, a 100%, 85,7% i 52,4% u KAPDB-2 grupi; p = 0,0345). Stopa 1-, 5-, i 10-godišnjeg preživljavanja metode iznosila je: 100%, 71,4% i 38,1% u KAPDB-1, a 100%, 85,7% i 76,2% u KAPDB-2 grupi (p = 0,0719). Kao nezavisni prediktori opšteg preživljavanja bolesnika na KAPD izdvojili su se: dijalizni staž, nivo serumskih triglicerida i skor kardiovaskularnog morbiditeta (kvantitativni sistem zbrajanja prisutnih sledećih parametara: ejekciona frakcija (EF) leve komore < 50%; IMT >1 mm; suženje lumena karotida > 50%; kalcifikovani ateromatozni plakovi na obe karotide; ishemijska bolest srca; cerebrovaskularni događaj i periferna vaskularna bolest sa ili bez gangrene). Kao nezavisan prediktor preživljavanja metode izdvojio se jedino dijalizni staž. **Zaključak.** Iako su bolesnici na KAPD sa biokompatibilnijim rastvorima pokazali statistički značajno bolje preživljavanje, ne možemo tvrditi da bioinkompatibilnost dijaliznih rastvora predstavlja značajan faktor rizika od preživljavanja bolesnika i same metode lečenja. Naime, multivarijantnom analizom kao prediktori opšteg preživljavanja bolesnika izdvojili su se samo dijalizni staž, nivo serumskih triglicerida i skor kardiovaskularnog morbiditeta, dok se za očuvanje peritoneumske membrane kao nezavisan faktor rizika prikazao samo dijalizni staž.

Ključne reči:
dijaliza, peritoneumska, ambulantna, kontinuirana; preživljavanje, analiza; rastvori, dijalizni; morbiditet; mortalitet; faktori rizika.

Introduction

Continuous ambulatory peritoneal dialysis (CAPD) has been a successful modality of renal replacement therapy for more than 30 years. CAPD, similarly to hemodyalisis (HD), has unsatisfactory mortality rate despite of all improvement of techniques that were described over the past decades [1]. The reason for high mortality is probably multifactorial: older age, co-morbidity, inflammation, malnutrition and atherosclerosis (MIA syndrome), decline in residual renal function (RRF) and increased peritoneal transport characteristics [2, 3]. Several reports in the literature suggest that racial and geographic difference may influence patients survival in dialysis populations [2]. Centre and patients characteristics may differ between study populations, and this may explain different literature reports. It is important to evaluate all predictors of patients and technique survival since correction of such risk factors may decrease morbidity and mortality and promote better quality of life in CAPD patients.

Annual morbidity rate of CAPD patients is more than 20% [4, 5], out of which 60% of patients die due to cardiovascular diseases (CVD) [6–8]. Progressive atherosclerosis significantly affect CV morbidity and mortality: 30%–60% of them suffer from calcification of hearth valves, while 70%–90% of patients suffer from calcification of coronary arteries [9–13]. Both prevalence and extent of calcification predicts CVD and total mortality in CAPD patients. It is also well known that MIA syndrome is an important predictors of mortality in PD patients [3, 14–16].

Recent developments in PD solution were aimed to improve their biocompatibility by changing buffers, osmotic agents and sterilization techniques, thereby reducing toxic effects on the immune system and functional deterioration of the peritoneal membrane [17]. Still, PD maintains a constant state of intraperitoneal inflammation which affects peritoneal membrane and has the potential to affect the efficiency of each PD dwell [18–21].

Currently, there are not many data on the effects of biocompatible solutions on survival. The long-term effects of pH neutral PD solutions that are low in glucose degradation products (GDP) are not clear. They seem to better preserve the peritoneal membrane and have less systemic effects than the conventional ones. Most of recent studies had a short follow-up (of only 6–12 months) for the confirmation of the effects of new biocompatible PD solutions on peritoneal transport, technique and patients survival [22].

The aim of the study was to evaluate a potential influence of biocompatibility of dialysis solutions on long-term CAPD patients and the techique survival.

Methods

This single-center cross-sectional study with prospective follow-up of the outcomes was performed in the Military Medical Academy Belgrade, where patients were treated by CAPD according to the mode of insurance: biocompatible PD solutions were covered by military insurance while patients with civil insurance were treated with bioincompatible PD solutions from the first PD start. The patients with military insurance were rarely officers (n = 5) but the members of their families (spouse, offspring). Pre-end stage renal disease (ESRD) treatment was not dependent on the type of insurance and those who had military insurance had all other access to medical care except of more expensive biocompatible CAPD solutions once when they reached ESRD.

The study included 42 stable randomly selected CAPD patients from both groups (26 men and 16 women) during the twelve years. Those with severe anemia (Hb < 10 g/L), history of or current systemic inflammatory disease or immunomodulatory therapy and malignant disease were excluded. Twenty one (50%) patients were treated with the standard bioincompatible PD solutions [conventional glucose-based, lactate-buffered solutions – Stay safe, ANDY-disc; Fresenius Medical Care, (the CAPDP-1 group)] while the remaining 21 (50%) of the patients were treated with biocompatible PD solutions [lower level of glucose degradation products (GDPs), lower concentration of Ca^{2+} and neutral pH – Fresenius Medical Care Stay Safe balance; Gambrosol Trio, (the CAPDP-2 group)]. There was no switch-over between modalities. There were no significant differences in prescription of statins, aspirin, erythropoietin, vitamin D and iron between the groups from starting CAPD until the time of analysis.

After 2.5 ± 0.6 years of CAPD starting, all the patients underwent echocardiography and B-mode ultrasonography of common carotid arteries CCA together with assessments of nutrition status, residual renal function, peritoneal solute transport and some biochemical parameters of systemic and local inflammation, and these variables were considered in the analysis of risk factors.

Data including age, gender and underlying renal disease were analyzed at the moment of starting CAPD. Data including residual renal function and peritoneal solute transport were observed after 2.5 ± 0.6 years of starting CAPD and were correlated with the presence of chronic inflammation, echocardiography data, B-mode ultrasonography of CCA data, parameters of malnutrition, peritoneal transport and cardiovascular score (CVS) which were determined after the same period of beginning on CAPD. The end-points of the study were patients death, transplantation, transfer to HD or the end of the study period in April 2009.

Residual renal function was estimated by measuring 24 h urine collection (residual diuresis) and serum level of a novel serum marker of the glomerular filtration rate – cystatin C by particle-enhanced nephelometric immunoassay (Dade-Behring's). Cystatin C in PD fluid was not measured**.** The normal average reference range of serum Cystatin C for patients without renal failure was 0.52–0.90 mg/L for women, and 0.56–0.98 mg/L for men.

High-sensitivity C-reactive protein (Hs-CRP) as acute-phase parameters of systemic inflammation, was measured by using the Tina-quant CRP (Latex) highly sensitive assay (Roche Diagnostics GmBH, Mannheim, Germany). The lower limit of detection for hs-CRP 0.01 mg/L. CRP values less than 5 mg/L was considered normal. A fasting venous blood samples were taken from the subjects before the morning exchange after a 12 h our fasting.

Effluent concentration of CA-125 as a marker of mesothelial cell mass and pro-inflammatory cytokine interleukin (IL)-6 as a marker of local inflammation were measured in overnight effluent in both groups of CAPD patients. Dialysate samples were taken immediately after the dwell. The effluent Ca-125 concentration was measured using an electrochemoluminescence immunoassay (CECLIA) (Lecsys 2010; Roche Diagnostics, Heidelberg, Germany), the sensitivity of which was 0.60 U/mL. The effluent CA-125 concentrations greater than 35 U /mL were considered as a good values.

Peritoneal level of IL-6 was determined by specific commercial ELISA kits (Biosource, Camarillo, CA, USA). The lowest threshold of detectability for IL-6 was 2 pg/mL.

The nutritional status of patients was assessed by measurement of serum albumin, total cholesterol and triglycerides, body mass index (BMI), anthropometric parameters and by subjective global assessments (SGA). Body mass index was calculated by the equation published elsewhere [23].

Anthropometric measurements included mid-arm circumference (MAC), triceps skinfold (TSF), and a calculated estimate of the mid-arm muscle circumference (MAMC) according to NKF K/DOQI Guidelines [23, 24]. SGA was based on methodology described by Kalantar-Zadeh et al. [24]. The data were weighed and the patients were classified in terms of three major SGA scores: 1 = well nourished, 2 = moderate malnutrition or 3 = severe malnutrition.

Peritoneal solute transport was investigated by peritoneal equilibration test (PET) and by measuring 24-h peritoneal ultrafiltration (UF, ml) using standard method described by Twardowski [25].

Echocardiography measurements were made by a single experienced cardiologist according to the recommendations of the American Society of Echocardiography [26] with Aspen-ACUSON device equipped with a 2.5 MHz probe. Cardiac valvular calcification was defined as bright echoes of >1 mm on one or more cusps of the aortic valve, mitral valve or mitral annulus.

B-mode ultrasonography of CCA was performed by using the ALOCA SSD 2000 system equipment with 7.5 MHz linear transducers. A trained sonographer evaluated intima-media thickness (IMT, mm), carotid narrowing degree (%) and the presence of carotid plaques in both CCAs 4 cm from the bulbs, within carotid bulbs and the first 2 cm of the internal and external carotid arteries. Plaques were defined as echogenic structures showing protrusion into the lumen with focal widening that was 50% greater than the IMT of adjancent sites. Highly echogenic plaques producing bright

white echoes with shadowing were considered to be calcifications. Such plaques were defined as representing arterial intimal calcification pattern.

Cardiovascular score included: ejection fraction (EF) of left ventricle < 40%; IMT > 1 mm; carotid narrowing degree > 50%, the presence of carotid plaques in both common carotide, ischemic heart disease, cerebrovascular event and peripheral vascular disease with or without amputation. The cardiovascular morbidity score for each patient was defined as the number of these domains affected, varying from score 0 to score 7.

Patients outcome included a reason of death: cardiovascular diseases (ishemic heart disease, cerebrovascular disease and peripherial vascular disease) and noncardiovascular diseases (peritonitis, multiorgan failure).

Patients survival analysis included data from the start of CAPD until the end of the follow-up period in April 2009 or date of death, censored at the time of renal transplantation and transfer to hemodialysis.

Technique survival analysis included data from the start of CAPD until the date of transfer to HD or at the end of a follow-up period in April 2009, censored at the time of renal transplantation and date of patients death.

Statistical calculations were performed using the SPSS software program. Data were expressed as percentages for discrete factors, and mean values for continuous variables. Medians were used for continues variables without normal distribution. Student's *t*-test (parametric data) and Kruscal Wallis test or Mann-Whitney (non-parametric data) were used to compare the subgroups. The χ^2 test was used to compare the nominal variables between different subgroups. Acturial survival rates were determined by the Kaplan-Meier method. A log-rank test was used to compare the patient and technique survival between the subgroups. The Cox proportional hazards model was used to identify the factors predicting patient mortality and technique survival. The Cox model for multivariate analysis was constructed by those factors significant at univariate analysis. In all the comparisons, a p value < 0.05 was considered statistically significant.

Results

In this paper we analyzed the patients divided in two groups according to the type of insurance. Even so, the selection bias was avoided since there were no significant differences between the groups in age, gender, underlying renal disease, residual renal function, ultrafiltration and peritoneal transport characteristics (Table 1). In addition, there were no differences between groups in comorbidity and previous medication [(including erythropoietin stimulating agents, angiotensin-converting enzyme (ACE) inhibitors, iron and vitamin D, social status and monthly income (data not shown)].

Table 1

General characteristics of the examined patients at the moment of analysis [age, gender and underlying renal disease at the moment of starting continuous ambulatory peritoneal dialysis (CAPD)]; other 2.5 ± 0.6 yearsfollowingstarting CAPD)

The observed parameters	The examined groups		*p*-value
	CAPDP-1	CAPDP-2	
Number of patients	21	21	/
Average age (years), $\bar{x}$ ± SD	60.5 ± 13.7	65.8 ± 12.2	NS
Gender, n (%)			
male	11 (52.4)	15 (71.4)	NS
female	10 (47.6)	6 (28.6)	
Cause of CRF, n (%)			
diabetic nephropathy	7 (33.3)	8 (38.1)	
chronic GN	2 (9.5)	2 (9.5)	
nephroangiosclerosis	8 (38.1)	10 (47.6)	NS
BEN	2 (9.5)	0 (0)	
nephrolithiasis	1 (4.8)	1 (4.8)	
unknown	1 (4.8)	0 (0)	
Residual diuresis (L/day), $\bar{x}$ ± SD	0.64 ± 0.72	0.65 ± 0.59	NS
Cystatin C (mg/L), $\bar{x}$ ± SD	6.23 ± 1.62	5.36 ± 1.31	NS
Peritoneal transport, n (%)			
low	3 (14.3)	5 (23.8)	
low average	9 (42.9)	12 (57.1)	NS
high average	7 (33.3)	3 (14.3)	
high	2 (9.5)	1 (4.8)	
Ultrafiltration volume (mL/24h), $\bar{x}$ ± SD	938.1 ± 563.0	892.2 ± 598.7	NS

CAPDP-1 – the group of patients treated by bioincompatible peritoneal dialysis solutions;
CAPDP-2 – the group of patients treated by biocompatible peritoneal dialysis solutions; CRF – chronic renal failure;
GN – glomerulonephritis; BEN – Balkan endemic nephropathy; rGFR – residual glomerular filtration rate; NS – not significant

At the moment of analysis (after 2.5 ± 0.6 years of starting CAPD) inflammatory markers in the serum and in peritoneal effluent were analyzed (Table 2). The mean value of serum hs-CRP was significantly lower in the CAPDP-2 than in the CAPDP-1 group, while there were no significant differences between the groups concerning the effluent level of IL-6 and CA-125.

Nutritional parameters are presented in Table 3. There were no significant differences between the groups in total serum cholesterol, triglyceride, albumin and BMI. By comparing mid-arm circumference, mid-arm muscle circumfer-

Table 2

Biochemical markers of inflammation for the examined patients at the moment of analysis (2.5 ± 0.6 years following starting continuous ambulatory peritoneal dialysis – CAPD)

The observed parameters	The examined groups		*p*-value
	CAPDP-1	CAPDP-2	
Markers of systemic inflammation			
hs-CRP (mg/L), $\bar{x}$ ± SD (median)	6.3 ± 4.5 (5.31)	3.7 ± 2.6 (3.53)	0.003
Markers of local inflammation			
effluent IL-6 (pg/mL), $\bar{x}$ ± SD (median)	135.6 ± 114.1 (84.8)	117.3 ± 79.8 (80.0)	NS
effluent CA-125 (U/mL), $\bar{x}$ ± SD (median)	30.3 ± 21.8 (24.04)	42.7 ± 32.4 (31.6)	NS

CAPDP-1– the group of patients treated by bioincompatible peritoneal dialysis solutions; CAPDP-2 – the group of patients treated by biocompatible peritoneal dialysis solutions; hs-CRP – high-sensitivity C-reactive protein; NS – not significant

Table 3

Nutritional parameters for the examined groups of patients at the time of analysis (2.5 ± 0.6 years folloving starting continuous ambulatory peritoneal dialysis – CAPD)

The observed parameters	The examined groups		*p*-value
	CAPDP-1	CAPDP-2	
Serum albumin (g/L), $\bar{x}$ ± SD (median)	30.2 ± 4.1 (30.0)	30.2 ± 3.7 (30.0)	NS
Serum total cholesterol (mmol/L), $\bar{x}$ ± SD (median)	6.1 ± 1.4 (5.83)	5.4 ± 1.3 (5.41)	NS
Serum triglycerides (mmol/L), $\bar{x}$ ± SD (median)	2.4 ± 1.3 (2.1)	2.4 ± 1.6 (1.92)	NS
Body mass index (kg/m^2), $\bar{x}$ ± SD (median)	24.8 ± 4.0 (25.05)	24.6 ± 1.9 (24.32)	NS
MAC (cm), $\bar{x}$ ± SD (median)	27.9 ± 4.0 (27.0)	28.4 ± 2.4 (29.5)	0.015
MAMC (cm), $\bar{x}$ ± SD (median)	22.7 ± 2.4 (22.3)	23.1 ± 2.9 (24.2)	0.002
Subjective global assessment, n (%)			
well nourished	6 (28.6)	18 (85.7)	
mildly malnourished	10 (47.6)	3 (14.3)	0.000
moderate to severe malnutrition	5 (23.8)	0 (0)	

CAPDP-1 – the group of patients treated by bioincompatible peritoneal dialysis solutions; CAPDP – the group of patients treated by biocompatible peritoneal dialysis solutions; MAC – mid-arm circumference; MAMC – mid-arm muscle circumference; NS – not significant

ence and subjective global assessment it was confirmed that the patients from the CAPDP-1 group had significantly worse nutritional status than those from the CAPDP-2 group.

Cardiovascular scores are presented in Table 4. Both groups of the patients had mean EF, in the normal range. Although the patients on CAPDP-1 solutions had higher frequency of valvular calcification, the difference between groups did not reach statistical significance. Significant differences between groups were observed in prevalence of left ventricular hypertrophy (LVH), CVS, IMT, the degree of carotid narrowing and calcified plaques of CCA.

Clinical outcome is shown in Table 5. At the end of follow-up, 57.1% of the patients in the CAPDP-1 group and 47.7% in the CAPDP-2 group died. The most frequent causes of death were cardiovascular diseases in both groups without a statistical significance.

Patients and technique survival rates are shown in Figures 1 and 2. By Kaplan-Meier analysis, it was revealed that patients who underwent CAPD by bioincompatible PD solutions had significantly lower survival than those on CAPD by more biocompatible solutions. The median duration of treatment (from the start of CAPD to the end of follow up period)

Table 4

Markers of cardiovascular morbidity for the examined patients at the moment of analysis (2.5 ± 0.6 years following starting CAPD)

The observed parameters	The examined groups		*p* value
	CAPDP-1	CAPDP-2	
IMT (mm), $\bar{x}$ ± SD	1.6 ± 0.5	1.2 ± 0.3	$p = 0.005$
Carotid narrowing degree (%), $\bar{x}$ ± SD	32.4 ± 16.5	12.9 ± 14.9	$p = 0.000$
Presence of calcified plaques, n (%)	20 (95.2)	13 (61.9)	$p = 0.003$
Ejection fraction (%), $\bar{x}$ ± SD	57.1 ± 7.1	59.9 ± 3.6	NS
Presence of LVH, n (%)	19 (90.5)	13 (61.9)	$p = 0.039$
Presence of valvular calcification, n (%)	15 (71.4)	9 (42.9)	NS
CVS, n (%)	1 (4.8)	1 (4.8)	
0			
1	0 (0)	4 (19.0)	
2	3 (14.3)	7 (33.3)	
3	5 (23.8)	6 (28.6)	$p = 0.012$
4	10 (47.6)	3 (14.3)	
5	2 (9.5)	0 (0)	
6	0 (0)	0 (0)	
7	0 (0)	0 (0)	

CAPDP-1 – the group of patients treated by bioincompatible peritoneal dialysis solutions; CAPDP-2 – the group of patients treated by biocompatible peritoneal dialysis solutions; IMT – intima-media thickness; LVH – left ventricular hypertrophy; CVS – cardiovascular score (see the text); NS – not significant

Table 5

Clinical outcomes for the examined patients

The observed parameters	The examined groups		*p* value
	CAPDP-1	CAPDP-2	
Follow-up duration (months), median	78	128	
Clinical outcomes, n (%)			
remained alive on CAPD	3 (14.3)	7 (33.3)	
transplanted	1 (4.8)	0 (0)	NS
transferred to HD and stayed alive	5 (23.8)	4 (19.0)	
died	12 (57.1)	10 (47.7)	
Cardiovascular causes of death, n (%)	7 (58.3)	8 (80.0)	
ishemic heart disease	6 (50.0)	4 (40.0)	
cerebrovascular disease	1 (8.3)	2 (20.0)	NS
peripheral vascular disease	0 (0)	2 (20.0)	
Non-cardiovascular causes of death, n (%)	5 (41.7)	2 (20.0)	
peritonitis	2 (16.7)	1 (10.0)	NS
multiorgan failure	3 (25.0)	1 (10.0)	

CAPDP-1– the group of patients treated by bioincompatible peritoneal dialysis solutions; CAPDP-2 – the group of patients treated by biocompatible peritoneal dialysis solutions; HD – hemodialysis; NS – not significant

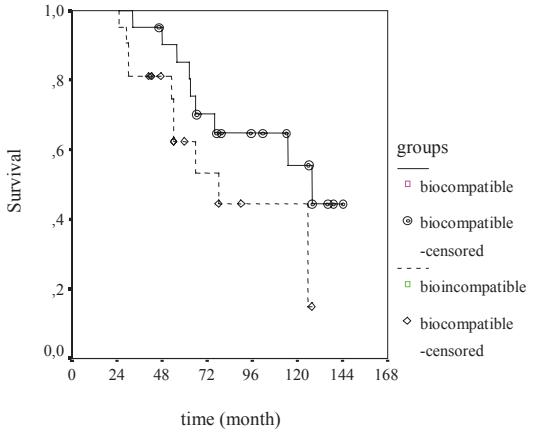

Fig. 1 – Kaplan-Meier survival curves for peritoneal dialysis patients treated by biocompatible and bioincompatible peritoneal dialysis solutions (Log- Rank; *p* = 0.0345).

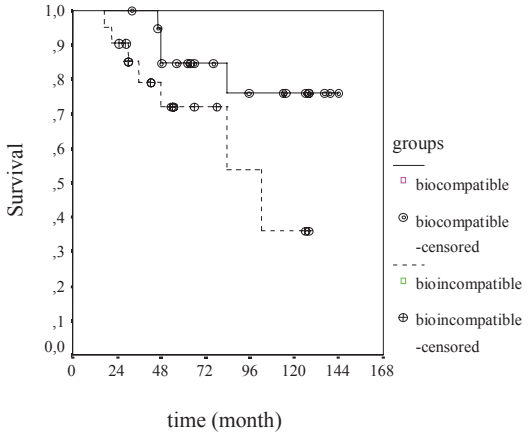

Fig. 2 – Kaplan-Meier survival curves of technique survival using biocompatible and bioincompatible peritoneal dialyis solutions (Log-Rank; *p* = 0.0719).

for the CAPDP-1 group was 78 months (range 30 to 128 months) while the median duration of the treatment for the CAPDP-2 group was 128 months (range 32 to 144 months).

Technique survival rate was not different between the groups (Figure 2). The median technique survival for the CAPDP-1 group was 102 months (range 30 to 128 months) while the median technique survival for the CAPDP-2 group was not affected (more than 50% of the patients in the CAPDP-2 group had functional peritoneal membrane and catheter at the end of the follow-up).

Predictors of patients survival are shown in Table 6. By Cox proportional hazards analysis, duration of dialysis, serum triglyceride and cardiovascular score were found to be independent predictors of overall patient survival.

Predictors of technique survival are shown in Table 7. By Cox proportional hazards analysis, only duration of dialysis was found to be an independent predictor of overall technique survival.

Discussion

In the present study, we compare the long-term effects of conventional glucose-based PD solutions and a new, neutral bicarbonate-/lactate-based PD solutions with lower level of glucose degradation products and lower concentration of Ca^{2+} on some markers of MIA syndrome and CAPD patients and the techique survival. This study showed a statistically significantly higher chronic inflammation, malnutrition and cardiovascular morbidity rate in patients treated by bioincompatible than patients treated by biocompatible dialysis solution. Mortality data revealed a similar 2-year-survival in both groups. However, with time patients who underwent CAPD by bioincompatible PD solutions had significantly worse survival than those on CAPD with biocompatible solutions. Although there was a trend toward better technique survival in the patients on CAPD by biocompatible solutions, a significant difference between the CAPDP groups was not confirmed by our study. Cox proportional hazards analysis confirmed that the duration of dialysis, serum triglyceride and cardiovascular morbidity score were independent predictors of overall patient survival, while the duration of dialysis was only independent predictor of overall technique survival.

Inspite big technical improvements during the last 20 years, morbidity and mortality rate of patients undergoing CAPD is still very high. Recent studies suggest that, during

Table 6

Univariate and multivariate Cox regression model on patient survival for the overall group of patients

Parameters	Univariate		Multivariate	
	RR (95%CI)	Significance	RR (95%CI)	Significance
PD solutions biocompatibility	0.403 (0.167–0.976)	0.044*	0.761 (0.283–2.048)	0.588
Gender	1.703 (0.715–4.056)	0.229	/	/
Average age	0.998 (0.973–1.023)	0.865	/	/
Duration of dialysis	0.568 (0.415–0.776)	0.000*	0.457 (0.307–0.680)	0.000*
C-reactive protein	1.105 (0.987–1.238)	0.083	/	/
Serum cholesterol	1.318 (0.942–1.842)	0.107	/	/
Serum triglycerides	1.382 (1.035–1.844)	0.028*	1.450 (1.067–1.969)	0.018*
Serum albumin	0.946 (0.850–1.053)	0.312	/	/
Cystatin C	1.103 (0.806–1.509)	0.539	/	/
Residual diuresis	1.012 (0.537–1.907)	0.971	/	/
Effluent IL6	0.997 (0.992–1.003)	0.327	/	/
Effluent CA-125	1.012 (0.997–1.028)	0.110	/	/
Peritoneal transport	1.006 (0.724–1.399)	0.969	/	/
Ultrafiltration volumen	1.000 (0.999–1.001)	0.889	/	/
Eject fraction	0.994 (0.940–1.050)	0.828	/	/
Presence of LVH	0.738 (0.297–1.838)	0.514	/	/
Presence of VC	1.993 (0.829–4.794)	0.123	/	/
IMT	0.434 (0.138–1.366)	0.153	/	/
Carotid narrowing degree	1.013 (0.994–1.033)	0.189	/	/
Presence of calcified plaques	0.959 (0.350–2.627)	0.935	/	/
BMI	0.963 (0.765–1.213)	0.748	/	/
MAC	0.909 (0.739–1.116)	0.361	/	/
MAMC	0.989 (0.804–1.217)	0.916	/	/
SGA	1.491 (0.985–2.259)	0.059	/	/
CVS	1.448 (1.058–1.981)	0.021*	2.095 (1.362–3.223)	0.001*

CI – confidence interval; RR – relative risk;* statistically significant; LVH – left ventricular hypertrophy; VC – valvular calcification; IMT – intima-media thickness; BMI – body mass index; MAC – mid-arm circumference; MAMC – mid-arm muscle circumference; CVS – cardiovascular score

Table 7

Univariate and multivariate Cox regression model on techique survival for overall group of patients

Parameters	Univariate		Multivariate	
	RR (95%CI)	Significance	RR (95%CI)	Significance
PD solutions biocompatibility	0.342 (0.099–1.184)	0.090	/	/
Gender	0.902 (0.237–3.432)	0.880	/	/
Average age	0.985 (0.952–1.020)	0.409	/	/
Duration of dialysis	0.598 (0.404–0.886)	0.010*	0.598 (0.404–0.886)	0.010*
C-reactive protein	1.095 (0.949–1.264)	0.216	/	/
Serum cholesterol	1.005 (0.631–1.598)	0.985	/	/
Serum triglycerides	0.921 (0.579–1.465)	0.727	/	/
Serum albumin	0.969 (0.828–1.135)	0.699	/	/
Serum cystatin C	1.193 (0.770–1.848)	0.431	/	/
Residual diuresis	0.920 (0.368–2.299)	0.859	/	/
Effluent IL6	0.971 (0.829–1.139)	0.720	/	/
Effluent Ca125	0.999 (0.991–1.006)	0.726	/	/
Peritoneal transport	0.821 (0.592–1.138)	0.236	/	/
Ultrafiltration volumen	0.993 (0.969–1.019)	0.601	/	/
Eject fraction	0.984 (0.918–1.056)	0.663	/	/
Presence of LVH	0.826 (0.241–2.830)	0.761	/	/
Presence of VC	0.819 (0.233–2.881)	0.756	/	/
IMT	2.023 (0.546–7.498)	0.292	/	/
Carotid narrowing degree	0.996 (0.967–1.026)	0.791	/	/
Presence of calcified plaques	1.269 (0.335–4.802)	0.726	/	/
BMI	1.248 (0.941–1.653)	0.124	/	/
MAC	1.317 (0.459–3.775)	0.608	/	/
MAMC	1.224 (0.908–1.650)	0.185	/	/
SGA	1.141 (0.568–2.293)	0.712	/	/
CVS	0.860 (0.581–1.273)	0.451	/	/

CI – confidence interval; RR – relative risk;* statistically significant; LVH – left ventricular hypertrophy; VC – valvular calcification; IMT – intima media thickness; BMI – body mass index; MAC – mid-arm circumference; MAMC – mid-arm muscle circumference; CVS – cardiovascular score

the first 2 years of follow-up, the survival rate of patients with chronic kidney disease who begin PD is the same as or better than those who begin HD. However, the majority of these studies show higher mortality rates in PD during the second year and thereafter [27, 28]. Different risk factors were reported to be important for outcome of patient on CAPD: age and race, underlying disease (diabetes), residual renal function, MIA syndrome and peritoneal membrane characteristics.

In general, age and the presence of diabetes at the beginning of the treatment are the main factors associated with coronary artery calcifications and mortality in dialysis patients [13, 28, 29]. Chow et al. [30] reported that diabetes mellitus was the strongest risk factor for sudden death after accounting for other cardiovascular and relevant risk factors. In our study, the age and the prevalence of diabetes mellitus were similar in both groups.

Residual renal function (RRF) during the first years of PD is an important factor of PD adequacy, contributing of 20%–50% a total solute clearance. In a recent reanalysis of the CANUSA study, there is clear evidence indicating higher contribution of RRF to the clinical outcomes of PD patients than peritoneal clearance. Namely, patients with RRF had better survival than those without [31]. Williams et al. [32] and Haag-Weber et al. [33] showed urine volume higher in patients treated with the new biocompatible PD solutions. Szeto et al. [34] analyzed the effect of the biocompatible PD solution (balance) in 25 randomized patients and found out the beneficial effect of those solutions on membrane characteristics and CRP; however, there were no differences between conventional and bicompatible solution concerning daily ultrafiltration and urine volume. Our patients had preserved RRF at the start of CAPD without a significant difference between the groups during the treatment (data not showen). Still, the contribution of a diminished ultrafiltration and subclinical fluide overload remains unexplored and may influence RRF in patients treated with biocompatible solutions [35].

Chronic inflammation may also play a major role in high cardiovascular mortality rate in CAPD patients [36]. Approximately 30%–50% of non-dialysis, hemodialysis and peritoneal dialysis patients had a state of chronic inflammation as defined by increased biochemical markers of the acute-phase response, including CRP or proinflammatory cytokines [37]. Components of dialysis solutions, especially GDPs, damage peritoneal cells and may trigger an inflammatory response. The use of a more biocompatible, neutral pH PD solution with a low concentration of GDPs was shown to result in significant reduction of intraperitoneal inflammation [32, 38, 39]. However, the study by Pejek et al. [40] showed no difference between a conventional solution (Dianeal) and a more biocompatible solution (Physioneal) in effluent macrophage inflammatory activation after a timed overnight dwell. Also, the systemic levels of IL-6 and hs-CRP did not differ between the two solutions [33, 40]. In our groups of patients, mean value of serum hs-CRP was significantly lower in the patients who underwent CAPD by biocompatible PD solutions than in the patients on CAPD treated with bioincompatible solutions, while parameters of local inflammation were similar between the CAPD groups. These findings are in agreement with our previous results that confirmed no difference in cytokines levels in patients treated with different PD solutions [41].

Protein energy malnutrition and muscle wasting are present in many patients with chronic renal failure and significantly influence patients outcome. This may be a consequence of uremia *per se* or related to co-morbid conditions [42]. Also, many studies report that inflammation may be an important cause of malnutrition [43]. Qureshi et al. [44] showed elevated serum CRP not only associated with hypoalbuminemia, but also more commonly with in malnourished patients as assessed by SGA of nutritional status. Zheng et al. [45] observed that GDPs in the PD solution are probably involved in the suppression of appetite and that the degree of inhibition is proportional to pH and glucose concentration. All our patients had similar values of serum total cholesterol, triglycerides, albumin and BMI. However, the mean values of mid-arm circumference, mid-arm muscle circumference and subjective global assessment were significantly better in the patients treated with biocompatible solutions than the patients on CAPD with bioincompatible solutions. This means that chronic peritoneal dialysis with bioincompatible solutions may influence muscle wasting.

The results of studies that evaluated the effects of novel more biocompatible solutions on peritoneal ultrafiltration (UF) rate and peritoneal solute transport are conflicting [46, 47]. These studies did not show that biocompatibility of PD solutions had significant influence on peritoneal UF rate and solute transport characteristics in a selected group of patients.

Cardiovascular complications are the major causes of morbidity and mortality in PD patients mainly due to cardiovascular calcifications and progressive atherosclerosis [4–13]. The present study shows a high overall cardiovascular morbidity rate in both groups of patients with statistically significant differences in the presence of LVH, all parameters of peripheral vascular disease and cardiovascular score between the groups. Since there were no differences between the groups in the incidence of diabetes, hypertension, ultrafiltration volume and medication, it is possible that biocompatible PD solutions might have beneficial effects on cardiovascular morbidity. Still, there may be numerous additional factors that may influence cardiovascular parameters including subclinical overhydration and others not included in this study.

In Western countries, cardiovascular disease is a leading cause of mortality in dialysis patients [6, 48, 49]. Lee et al. [50] reported that infectious disease was the leading cause of mortality for dialysis patients and caused significantly more mortality in HD than in PD patients. In our study, the most frequent causes of death were cardiovascular diseases in both groups without statistically significant difference.

Our study presents a better patients survival rate using biocompatible PD solutions and similar or worse long-term patients survival rate using bioincompatible PD solutions than in several reports [2, 51–56]. One of the explanations of better results in our study could be a small number of the selected groups and elimination of patients with severe comor-

bidity (see excluding criteria in the section Methods) and using evidently better biocompatible CAPD solutions.

This study also presents the better overall technique survival rate than in several reports [2, 48, 51–56]. Thus, 1-, 2-, and 3-year technique survival rates were 86.0%, 73.6% and 60.5%, respectively, for Korean, and 89.%, 65.9% and 51.9%, respectively, for Swedish patients [2]. In our patients, 1-, 2- and 3-year technique survival rates were: in the CAPDP-1 group 100%, 90.5%, 80.9%, respectively, and in the CAPDP-2 group 100% for all the three periods. Even so, the difference between the groups did not reach a statistical significance and one of the explanations could be the small number of patients in both groups. Long-term technique survival on CAPD by bioincompatible PD solutions was addressed by many authors, but there were no studies to confirm the effects of new biocompatible PD solutions on the technique and patients survival after a follow-up period of more than two years [22]. In our study we analyzed the effects of new, neutral PD solutions on the technique and patients survival after a follow-up period of up to 12 years.

By Cox proportional hazards analysis we showed duration of dialysis, serum triglyceride and cardiovascular score to be independent predictors of overall patients survival. Only duration of dialysis was found to be independent predictor of overall technique survival.

The present study has to be interpreted in the light of several weak points. The study population included patients with military insurance and those with civil one. Although there were no significant differences between them, one may raise the question about selection bias. Cross-sectional analysis of potentional risk factors does not provide more dynamic data that may change with the time on CAPD. A small number of patients may influence statistical significance and we believe that inclusion of a higher number of patients may contribute to the final conclusion. Apart from those presented, there may be more parameters not included in this study that could reveal the effects of biocompatibility of PD solution on parameters of MIA syndrome and patients and technique survival.

Conclusion

Patients undergoing CAPD have high cardiovascular morbidity. Chronic inflammation revealed by hs-CRP, protein energy malnutrition and peripheral atherosclerosis had higher prevalence in those treated by bioincompatible PD solutions. Patients survival after a 2-year-follow-up is significantly better if patients treated by biocompatible solutions. No difference in the technique survival is observed between the groups of our patients at any point of time.

Although patients treated with biocompatible solutions showed a significantly better survival, Cox regression analysis did not confirm that biocompatibility of PD solutions was independent predictor of patients and the technique survival.

In our setting, duration of dialysis, serum triglyceride and cardiovascular score significantly predicted an overall CAPD patients survival, while duration of dialysis was found to be the only independent predictor of overall technique survival. Further well designed and controlled studies on higher number of patients are needed to highlight the role of biocompatibility in outcome of patients on chronic peritoneal dialysis.

Disclosure

The authors declare that no financial conflict of interest exists. The authors alone are responsible for the content and writing the paper.

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