Biocompatible peritoneal dialysis solutions: do they indeed affect the outcome?*

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ABSTRACT
Numerous studies have confirmed beneficial effects of polyglucose dialysis solution (PG ‑ DS), an amino acid dialysis solution (AA ‑ DS), and bicarbonate (bic) or bicarbonate/lactate (bic/lac) buffered solutions on selected components of peritoneal bioavailability or clinical parameters of peritoneal dialysis (PD) patients. Few adverse effects have also been described. A question arises whether these solutions affect the PD outcome. A better controlled fluid status of PD patients associated with the use of PG ‑ DS has been shown in a double ‑ blind randomized controlled trial. Continuous cyclic PD patients treated with the PG ‑ DS did not show changes in solute kinetics and peritoneal membrane markers remained unaltered. The use of PG ‑ DS in anuric automated PD patients was associated with less impaired membrane function. A prospective, randomized, controlled study on the AA ‑ DS in malnourished continuous ambulatory PD patients did not show significant effects of the AA ‑ DS on patient survival, hospitalization rate, C ‑ reactive protein levels, total urea Kt/V, ultrafiltration and drop ‑ out rates, but nutritional status improved or was stable. Improved acid ‑ base balance with bic ‑ buffered solutions was shown in patients treated with automated PD or continuous PD. A registry ‑ based study suggests better survival of patients treated with a neutral pH, low glucose degradation product solution, but there were no differences in dialysis technique survival, peritonitis ‑ free survival, or peritonitis rates. However, reduced peritonitis rate was also reported with the use of bic/lac solutions. Current concepts of PD solutions involve efforts to use fluids which combine the advantages of PG ‑ DS, AA ‑ DS and bic ‑ buffered solutions. Large ‑ scale studies should be continued to improve biocompatibility of peritoneal solutions and to establish their effect on the clinical outcome.

At the end of the 20th century new peritoneal dialysis (PD) solutions were introduced in hope of improving quality of life and survival of patients treated with PD. A solution with glucose polymers (PG ‑ DS) was designed to enhance ultrafiltration over the long dwell for the better removal of excess water; a solution containing amino acids (AA ‑ DS) was expected to affect protein malnutrition, and solutions with neutral pH and low levels of glucose degradation products (GDP) were meant to protect the peritoneal membrane against the combination of low pH, high lactate levels and harmful effects of GDP. Regardless of specific indications for each solution, all are considered as more biocompatible comparing to standard high glucose and low pH solutions, buffered with lactate.

Biocompatibility of PD solutions is related to their more physiological pH, lower osmolarity, a decreased load of glucose and lower content of GDP as compared to standard solutions. A decreased load of glucose, despite metabolic consequences regarding multiple tissues and organs, contributes to reduced formation of Amadori albumin and advanced glycation end products (AGE) in the peritoneum. Lower content of GDP protects against direct harmful effects of GDP and also leads to a reduction in AGE accumulation in the peritoneum because GDP enhance AGE formation.

More biocompatible PD solutions should prevent or diminish changes in the peritoneal membrane occurring in the course of PD. Normal peritoneal membrane becomes thicker due to fibrosis, neoangiogenesis and accumulation of AGE. On the other hand, mesothelial cell mass decreases and the area of mesothelial denudation...
can be shown. Numerous in vitro, ex vivo and in vivo studies that addressed the issue of biocompatibility supported hopes related to the introduction of new solutions. Benefits of more biocompatible solutions include improved mesothelial cell proliferation and better preserved mesothelial cell mass, an intact mesothelial cell layer, improvements in viability of mesothelial cells, neutrophils and macrophages, especially augmented phagocytic activity, less angiogenesis in the parietal peritoneum and a reduction in fibrosis in the mesentery (~50%) and in the parietal peritoneum (~25%), reduced bacterial survival and less damage to cultured liver cells.

Benefits were shown especially with neutral pH solutions and the AA-DS. Comparisons of the influence of PG-DS and standard fluids on proliferation, morphology and secretory function of mesothelial cells provide various results. In some experimental studies a 7.5% PG-DS substantially restrained the normal process of mesothelial cell repopulation and induced repair with the connective tissue. The harmful effects of PG-DS were usually reported as smaller or comparable to those associated with a 4.25% glucose solution.

In studies evaluating effects of biocompatibility of peritoneal solutions, each new solution is analyzed separately. In clinical practice only neutral pH dialysis solutions can be exclusively used in the PD regimen, whereas the PG-DS and AA-DS are at present allowed only for 1 exchange daily. Thus, the clinical effects of the 2 latter solutions are influenced by fluids used for the remaining daily exchanges, usually still performed with standard solutions. A question arises how all these more biocompatible dialysis solutions influence parameters important for treatment with PD, and how they influence the outcome measured in the so-called hard endpoints. The answer for this question 1 in results of prospective, randomized, long-term clinical trials. Currently available studies are focused on parameters of peritoneal transport as indicators of the time-dependent increment in peritoneal permeability, parameters of peritoneal membrane viability, indices of local and systemic chronic inflammatory state, peritonitis rate, survival of patients and prolongation of PD treatment and evaluation of usability to specific targets designed for each solution. The main results related to these key problems will be presented.

Influence on peritoneal transport Peritoneal transport increases in the course of PD. It was also shown with the use of PG-DS. However, in patients treated with cyclic continuous PD (CCPD), having still preserved residual renal function, peritoneal transport measured using the mass transfer area coefficient (MTAC) for urea, creatinine, uric acid and glucose, remained unchanged during 2 years follow-up and was not significant between the groups treated using the PG-DS for daytime exchange and the group using glucose solution for daytime exchange. Moreover, in the European Automated Peritoneal Dialysis Outcomes Study (EPOS), performed in functionally anuric patients, peritoneal transport increased after 2 years of examination, independently on solutions administered for treatment, but patients treated with the PG-DS for daytime exchange showed lower peritoneal permeability than patients who used only glucose solutions, although patients using the PG-DS showed significantly higher peritoneal permeability at the beginning of the study. This prospective, but not randomized study shows that the PG-DS slows development of peritoneal permeability, at least under circumstances in which this process may be more enhanced due to high glucose levels used to achieve appropriate ultrafiltration in anuric patients.

A short (8-week) prospective, randomized study did not show the effect of AA-DS on peritoneal permeability in the PD capacity (PDC) test. These data are compatible with results obtained by Li et al. during an appropriate follow-up, published in 2003. However, the study by Li et al. with 3 years’ follow-up demonstrated an increase in peritoneal permeability from 6 to 30 months of treatment with the AA-DS, with higher values of MTAC of creatinine (but not urea) compared with results obtained for patients treated with standard solutions.

Solutions with neutral pH, likewise standard solutions, showed no effect on peritoneal permeability in prospective, randomized studies lasting from 8 weeks to 2 years.

Preservation of mesothelial cell mass In patients treated with the PG-DS a decrease in peritoneal mesothelial cell mass cannot be excluded because cancer antigen (CA) 125 levels in dialysate tended to decrease and CA 125 dialysate/plasma (D/P) was significantly lower after 2 years of treatment with the PG-DS. However, there were no significant differences between groups when the analysis of variance (ANOVA) was used in statistical analysis.

The AA-DS, which also has a more physiological pH as compared to standard solutions, in a prospective, randomized study the AA-DS was associated with an increase in the dialysate CA 125 level, suggesting successful remesothelialisation following damage due to the previous use of glucose solutions. However, exposure to the AA-DS was not more than 8 weeks.

Administration of neutral pH/low GDP solutions resulted in the higher level of CA 125 in dialysate. It was shown with the use of lactate-buffered solutions prepared in three- or two-compartment bags, with bicarbonate-lactate (bic/lac) solutions and with bic-buffered solutions. This beneficial effect was observed up to 2 years of the study. A withdrawal of a more biocompatible solution resulted in a decrease in peritoneal mesothelial cell mass. There is no data comparing effects of various neutral pH solutions in a single prospective study.
Secretory function of the peritoneal membrane
Parameters of secretory function of the peritoneal membrane, as shown for the aminoterminal propeptide of type III procollagen (PIIIINP), did not change during 2 years of PG-DS administration for daytime exchange in patients with preserved residual renal function treated with CCPD.\textsuperscript{21,22} These results were not different from those shown during the treatment with glucose solutions alone. The administration of a neutral pH/low GDP solution for 2 years resulted in an increase in PIIIINP in dialysate.\textsuperscript{5,15} These results were interpreted by authors as indicating a better function of peritoneal tissue.\textsuperscript{25} However, in cultured mesothelial cells secretion of PIIIINP was greater with less biocompatible solutions, and was related to higher glucose levels and higher content of GDP in the solution.\textsuperscript{30} These data indicate an unsolved interpretation difficulties by changes in the examined peritoneal markers.

Inflammatory state and peritonitis rate Patients treated with the PG-DS or AA-DS showed an increase in the interleukin 6 (IL-6) level in dialysate.\textsuperscript{23,31} It is discussed again whether such an increase represents enhanced chronic inflammation in the peritoneum, or it is a sign of less cellular inhibition or better preservation of cytokine release during glucose-free solutions. On the other hand, in 2 prospective, randomized studies\textsuperscript{5,27} a bic (25 mmol/l)/lac (15 mmol/l) solution used instead of an acidic lac (40 mmol/l) solution led to a decrease in IL-6 levels in dialysate. With a standard lac solution IL-6 levels increased in dialysate between the 1st and 5th months of the study whereas with a bic (25 mmol/l)/lac (15 mmol/l) solution IL-6 levels decreased during 1 month and the lower IL-6 level was observed to the analysis performed after 5 months of treatment.\textsuperscript{5} However, administration of a bic (25 mmol/l)/lac (15 mmol/l) solution to patients receiving the PG-DS and AA-DS did not prevent an increase in the IL-6 level in dialysate.\textsuperscript{31}

In prospective, randomized studies patients receiving the PG-DS for 8 weeks showed an increase in serum C-reactive protein (CRP).\textsuperscript{22} However, in 2003 bacterial peptidoglycan was discovered in the PG-DS and, at present, only solutions with the peptidoglycan level lower than 10 ng/ml are allowed to be used in patients.\textsuperscript{23,34} It cannot be excluded that even studies published in 2005 could be performed using solutions with uncontrolled, high content of peptidoglycan.\textsuperscript{35}

The AA-DS, administered for 3 years in malnourished Chinese patients, did not cause an increase in serum CRP, which was not significantly different from CRP in patients using a standard solution.\textsuperscript{34}

During the 3-year treatment with a bic dialysis solution (34 mmol/l) in a prospective, but not randomized study, serum CRP levels did not change significantly. Patients using standard solutions showed an increase in serum CRP levels during this 3-year follow-up, but the change was accompanied by higher peritonitis rate in the standard group compared to the bic group.\textsuperscript{36} In a 1-year randomized clinical study serum CRP levels even decreased when the solution with neutral pH and low GDP content in double-chamber bags was used. Changes in serum CRP levels in this study were not significant in the standard group and peritonitis-free survival was similar in the standard group and the group treated with neutral pH solutions.\textsuperscript{39}

As it was observed in the study by Montenegro et al.,\textsuperscript{24} lower peritonitis rate was also shown in patients treated for 1 year with a bic (25 mmol/l)/lac (15 mmol/l) solution instead of a standard lac (40 mmol/l) solution in a prospective, randomized study.\textsuperscript{38} Analysis of 121 cases of peritonitis, which occurred in the years 2002–2005 in 1 hospital in London, also revealed lower peritonitis rate (1 episode per 52.5 patient-months) in patients treated with a bic (25 mmol/l)/lac (15 mmol/l) solution compared to peritonitis rate (1 episode per 26.9 patient-months) in patients treated with standard lac solutions.\textsuperscript{37} Solutions with neutral pH, but not containing higher amounts of bic, did not change significantly peritonitis rate.\textsuperscript{29,38}

Treatment with the PG-DS for 6 months in the prospective, randomized, controlled Multicentre Investigation of Icodextrin in (continuous) Ambulatory Dialysis (MIDAS) did not influence peritonitis rate compared to standard solutions.\textsuperscript{39} The Dextrin in Ambulatory Peritoneal Dialysis in Amsterdam (DIANA) did not observe any significant difference in peritonitis rate in the 2-year study in patients treated with CCPD with standard solutions only or with the PG-DS for daytime exchange.\textsuperscript{22} Retrospective studies suggested low peritonitis rate in continuous ambulatory PD (CAPD) patients using the AA-DS,\textsuperscript{40} but a 3-year prospective study did not confirm this observation.\textsuperscript{74}

Mortality rate During a 2-year treatment with the PG-DS mortality rate was significantly lower in patients using the PG-DS instead of glucose 1 for daytime exchange, but the DIANA Group considered this as a coincidence.\textsuperscript{22} Mortality rate was identical in malnourished Chinese patients either using or not using the AA-DS for 3 years.\textsuperscript{42} A Korean study, based on registry of over 2000 patients treated with PD, showed lower mortality rate in patients using lactate-buffered, but neutral pH, low GDP solutions instead of standard lactate solutions. In a multivariate cyclooxygenase regression model, including age, diabetes and gender, the survival advantage of a more biocompatible solution persisted.\textsuperscript{38} The number of deaths during a 3-year prospective, but not randomized study, was also lower when a bic (34 mmol/l) dialysis solution with pH 7.4 and low GDP content was used and compared to standard solutions.\textsuperscript{38} These results suggest that more physiological pH and low content of GDP in dialysis solutions may contribute to prolongation of patient life-time, however, prospective, randomized studies have to confirm these observations.
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**Peritoneal dialysis technique survival**
Clinical data indicate that the PG-DS extends duration of CAPD treatment, but there are no prospective, randomized studies to support these observations. Technique survival in 3-year studies was similar in patients treated with the AA-DS vs. standard solutions24 or treated with neutral solutions vs. standard solutions.38

**Effects related to specific targets of peritoneal dialysis solutions**
Results of prospective studies confirm beneficial effects of the PG-DS on ultrafiltration for at least 0.5–2 years in nighttime exchanges in CAPD patients and in daytime exchanges in CCPD patients.22 Improved clinical parameters (stable body mass, less risk of edema) were also reported for at least 1 year by the Icodextrin Study Group.

Prospective, randomized studies confirmed the expected influence of AA-DS on the improvement in or maintenance of nutritional status in malnourished PD patients, especially women, as shown here for lean body mass and body mass index. Treatment of malnourished patients with standard solutions for 3 years caused further deterioration of nutritional parameters. In patients treated with the AA-DS an improvement in nutrition was accompanied by a decrease in serum triglyceride levels.

The clinical benefits of PD solutions with neutral pH include correction of uremic acidosis and lower peritonitis incidence and lower peritonitis rate of patients using these solutions. Long-term (over 3 years) prospective, randomized studies are needed to elucidate the issue as to whether more biocompatible PD solutions may prolong patient survival on PD treatment.

**Side effects**
Treatment with more biocompatible solutions has also some side effects. The main clinical disadvantages of PG-DS include sterile peritonitis (pseudoperitonitis), skin reactions, a decreased serum sodium level with an increased osmolar gap and increased serum levels of polyglucose metabolites.

The clinical disadvantages of AA-DS include an increased generation of urea and uric acid, elevated plasma homocysteine levels, gastrointestinal symptoms and decreased serum bic levels.

The clinical disadvantages of dialysis solutions with physiological pH occur very seldom and include metabolic alkalosis, occasionally observed with solutions containing higher bic levels (39 mmol/l).

**Combined effects of the PG-DS, AA-DS and neutral pH/low GDP solution**
Trials designed to show the advantages of PG-DS, AA-DS combined with those of neutral solutions have been published. Treatment of new CAPD patients with the AA-DS for 1 exchange, the PG-DS for 1 exchange and neutral solutions for 2 remaining exchanges daily for 30 weeks did not result in significant differences in dialysis efficiency, ultrafiltration, body weight, blood pressure, urine volume and laboratory blood tests, including hemo­globin, sodium, potassium, calcium, phosphorus, albumin, bic, lipid profile, glucose, glycated hemoglobin, as compared to respective results obtained for patients treated with standard solutions. Peritoneal transport, evaluated using the (D/P) ratio of creatinine and the ratio of dialysate glucose to baseline dialysate glucose (D/Dc) in the peritoneal equilibration test, was however significantly higher with the PD regimen based on new solutions. On the other hand, mesothelial cell mass expressed by dialysate CA 125 levels decreased less after initiation of CAPD with new solutions and remained higher during the entire study period.

**SUMMARY**
Current evidence provides support for using biocompatible solutions that have been designed to meet specific clinical needs (PG-DS for enhancement of ultrafiltration in long dwells, AA-DS for an improvement in or maintenance of protein nutrition, neutral solutions for correction of metabolic acidosis and in cases of low tolerance of acidic solutions). A common use of neutral pH/low GDP solutions for PD instead of standard lac-buffered solutions is reasonable because there is evidence based on prospective, randomized studies showing better preservation of peritoneal cell mass, less pronounced systemic inflammation and lower peritonitis rate of patients using these solutions. Long-term (over 3 years) prospective, randomized studies are needed to elucidate the issue as to whether more biocompatible PD solutions may prolong patient survival on PD treatment.

**REFERENCES**
Biozgodne płyny do dializy otrzewnowej: czy rzeczywiście poprawiają rokowanie?*

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SŁOWA KLUCZOWE
aminokwasy, biozgodność, płyny dializacyjne, polimery glukozy, wodorowęglan

STRESZCZENIE