Peritoneal dialysis solutions and patient survival: does wishing make it so?

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In this issue of Nephrology, Dialysis and Transplantation, Lee and colleagues [1] compare outcomes of Korean peritoneal dialysis (PD) patients who received standard dialysis fluid vs newer, ‘biocompatible’ dialysis solutions. This very interesting report found no significant difference in outcome of PD technique survival or its complications, such as peritonitis. However, those who received the new solution had a reduced risk of death. The authors suggest that the newer dialysis solutions may lead to sustained reduction in circulating levels of advanced glycosylation endproducts (AGEs), with a concomitant reduction in microvascular and macrovascular disease. Furthermore, the authors point to downstream effects of AGE binding with its receptors (RAGE), and suggest that reduced AGE production with new solutions could be followed by a parallel decline in the AGE–RAGE production of mediators of inflammation and fibrosis.

The authors reported similar findings last year [2]. In the previous report, they noted the weakness inherent in an uncontrolled, observational study, and quite correctly concluded that an ‘appropriately designed, randomized, controlled clinical trial’ was needed [2]. However, instead of proceeding with such a study, they report herein the results of the same observational study, with two modifications: firstly, the period of observation has been extended another 18 months. Secondly, the sub-cohort of patients who started PD on standard solution and were subsequently changed to the new, ‘biocompatible’ solution during the period of observation are now removed from the analysis, whereas they were included in the ‘intention to treat’ analysis in the first publication [2]. This is important, because the ‘excluded’ 305 patients who switched solutions had remarkable survival of 96, 89 and 87% at 1, 2 and 3 years. Had they not been excluded, these 305 patients would have counted as part of the standard solution group, and would have improved the overall survival of the remaining 514 patients in that group.

Who gets the expensive stuff?

There is no information as to what determined which patients received which dialysis solution in this non-randomized study. Those prescribed the biocompatible solution appeared to be healthier. The new-solution group was, on average, more than 2 years younger than those in the standard solution group. Two-thirds of the group receiving the newer solution came from centres with greater PD experience, compared with 44% in those treated with standard dialysate. Both younger age [3] and centre experience [4] is associated with better survival. The authors calculated that younger age alone could have accounted for almost half of the 39% reduced risk of death with the ‘biocompatible’ dialysate. The additional contribution of centre effect was not stated. It is clear that the two groups were not comparable, and the survival advantage could lie principally in patient and centre characteristics, and not the composition of dialysis fluid [5].

How could new dialysis solutions improve survival?

Aside from using the newer products in healthier patients, could the solutions themselves improve survival? The authors noted no difference in technique survival, so it was not the hazard effect associated with modality change. Furthermore, there was no difference in peritonitis rates. The authors postulate two principal mechanisms: preservation of residual kidney function (RKF) and the systemic effect of absorbed glucose degradation products (GDPs).
Residual kidney function

The amount of residual kidney function is a consistent and powerful predictor of survival in peritoneal [and haemodialysis (HD)] patients [6–8]. Explanations for this include the contribution of renal salt and water excretion to the maintenance of euvolement, the intrinsic anti-inflammatory effect of kidney function, and renal middle-molecular-weight toxin excretion (reviewed in [9]).

Although RKF was not measured in this study, the authors contend that another study, the Euro-Balance Trial, found better preservation of RKF in those using a biocompatible dialysis solution [10]. It is worthwhile to examine this contention more closely, since it has become ‘received wisdom’. In this well-designed randomized study, patients received 12 weeks of either standard or ‘biocompatible’ peritoneal dialysate, and then crossed over to the other solution. The primary end point was the concentration of CA125 in the dialysis effluent. Among the secondary end points were peritoneal membrane function and urine volume. Interestingly, patients became more rapid transporters on the ‘biocompatible’ solution. The dialysate to plasma creatinine ratio increased from 0.59 to 0.63 ($P = 0.008$) on the ‘biocompatible’ solution, and decreased reciprocally when patients crossed over to the standard dialysate (0.60 to 0.56, $P = 0.0003$). Demonstrating good internal consistency, ultrafiltration fell more than 350 ml/day with the new solution, and improved when patients changed to the standard solution.

Urine volume reflects extracellular fluid volume status and peritoneal ultrafiltration [11]. Therefore, it is perhaps not surprising that the reduced ultrafiltration associated with use of the ‘biocompatible’ dialysate lead to increased urine volume (and a concomitant increase in small solute excretion through relative hypervolaemia). This series of events does not necessarily involve improvement in RKF. Indeed, using that line of thinking, one would have to postulate, in the patients who changed from standard to new solution and experienced an increase in urine volume, not preservation, but resurrection, of residual kidney function. It is a plausible hypothesis that diminished absorption of toxic metabolites from ‘biocompatible’ peritoneal fluid could help preserve RKF. Unfortunately, it has not been convincingly demonstrated.

Reduction in GDP absorption and systemic glycation

The second explanation for the improved survival advanced by the authors is that the new solutions have lower levels of GDPs. It follows that there would be less absorption of these byproducts and a concomitant reduction in systemic formation of AGEs, leading to a reduction in AGE-associated vasculopathy, and less AGE–RAGE interaction. None of these parameters was measured in the current report, but once again the authors refer to the Euro-Balance study [10]. Serum levels of the AGEs carboxymethyllysine (CML) and imidazolone were measured in a subset of the patients at baseline, and at the completion of 3 months treatment with each solution. While serum levels of imidazolone increased and decreased relative to the use of standard and ‘biocompatible’ solution, the absolute levels after the first 3 months of standard dialysate (11.83 μg/ml) in the first group were virtually identical to levels after the first 3 months of new solution in the second group (11.81 μg/ml).

Importantly, elevated plasma levels of AGEs are not just the result of absorption of glucose or GDPs from PD fluid, but are a part of chronic kidney disease. In a study of CML levels in patients receiving different combinations of HD and haemofiltration, plasma levels, using what seems to be the same assay, were as high or even higher than those in PD patients in the Eurobalance study [12]. This would suggest that many of the plasma AGEs are a result of the uraemic state itself and unrelated to PD fluid. Indeed, the much-quoted study by Zeier et al. [13], of standard vs low GDP solutions, showed that plasma CML levels were not that different from each other, and are similar to those seen in HD patients. Another study that compared plasma levels of glycation free-adducts reported mean CML levels that were higher in HD patients pre-dialysis, compared with levels in PD patients [14]. Finally, to add even more confusion and uncertainty to the discussion, higher CML levels in HD patients has been associated with a survival advantage [15]. Clearly, meaningful interpretation of plasma values is not simple, and many circulating glycation products appear to be independent of PD solutions.

Wishing doesn’t make it so

PD is an excellent, practical, cost-effective treatment for chronic kidney disease. Believers in this modality eagerly await the ‘next big thing’ to advance the therapy further. In the meantime, our PD and HD patients continue to succumb to cardiac disease and sepsis. Biocompatible solutions were not the result of a spontaneous outcry from nephrologists and patients to reduce GDPs and AGEs. In vitro and in vivo studies suggest that the solutions could extend the longevity of the peritoneal membrane. However, much of the enthusiasm, in part driven by industry, that these solutions will affect other meaningful outcomes remains to be proven, as Lee et al. [2] originally suggested, by well-done randomized, controlled studies.

Conflict of interest statement. None declared.

(See related article by Lee et al. Nephrol Dial Transplant 2006; 21: 2893–2899.)

References

Oxidative stress and atherosclerosis in early chronic kidney disease

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Oxidative stress and cardiovascular disease: fundamental aspects

The chemical basis of oxidative stress

Reactive oxygen species (ROS) are intermediary metabolites that are normally produced in the course of oxygen metabolism. Under physiological conditions, ROS play a critical role as signal molecules, and ROS produced by activated leucocytes and macrophages are essential for defence against the invading micro-organisms. In addition to a mitochondrial origin, ROS can be generated by a great number of enzymes including oxidases, cyclo-oxygenases and lipoxygenases. Normally, ROS are contained by a wide array of antioxidant enzymes and endogenous and dietary antioxidants. The excess production of ROS or impaired antioxidant defense capacity leads to oxidative stress, in which uncontained ROS cause oxidation of macro-molecules, tissue damage and dysfunction.

The primary ROS produced in the body is superoxide anion ($\cdot O_2^-$) generated from a one-electron reduction of molecular oxygen. The nicotinamide adenine dinucleotide phosphate oxidase or NADPH oxidase is the main source of $\cdot O_2^-$ in mammalian cells [1]. NADPH oxidase is a multicomponent enzyme that has a membrane portion collectively known as cytochrome b$_{558}$, which is inactive until it is associated with the cytosolic components. Steady-state levels

References


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