Preserving residual renal function in peritoneal dialysis: volume or biocompatibility?

Simon J. Davies

Institute of Science and Technology in Medicine, Keele University and Department of Nephrology, University Hospital of North Staffordshire, Stoke-on-Trent, Staffordshire, UK

Correspondence and offprint requests to: Simon Davies; E-mail: simondavies1@compuserve.com

Leaving life-style issues aside, preservation of residual renal function (RRF) is seen as one of the main clinical benefits of peritoneal dialysis (PD) as a treatment modality choice. The majority of studies have indicated that RRF is relatively well preserved in comparison to haemodialysis (HD) [1,2] and two major hypotheses have emerged to explain this difference: (i) relative stability of volume status—perhaps even a tendency to develop hypervolaemia in PD compared to HD, where fluctuations in volume are common, especially when attempts are made to control blood pressure principally by manipulation of volume and (ii) the biocompatibility of the dialysis fluids. In the case of HD, there is evidence that ultrapure dialysate preserves RRF [3], whereas in PD it has been suggested that the newer biocompatible fluids, which contain reduced levels of glucose degradation products (GDPs), lead to reduced circulating levels of these potentially nephrotoxic substances [4].

This volume of *Nephrol Dial Transplant* contains two articles that address the issue of preservation of RRF in PD patients that shed further light on this debate. Liao and colleagues presented data on RRF from a large cohort study of Taiwanese PD patients, identifying factors associated with its preservation, whereas the randomized controlled trial from Kim *et al.* reported the effect of a biocompatible low GDP solution on a number of endpoints, including RRF.

**CANUSA** was the seminal study that drew attention to the importance for residual renal function in PD patients. This only became clear, however, on re-analysis of the study in 2001 [5] following the reports from single-centre studies such as the Stoke PD Study [6] that it was the RRF component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival. Because RRF changes with time on treatment, CANUSA treated it as a time-related component and not the peritoneal small solute clearance that was associated with survival.
remaining on PD with better RRF [9]. Even in single modality studies, this presents problems: if there is a belief among clinicians that PD is not a sufficient therapy in the absence of RRF, then a similar selection pressure will apply and thus more rapid loss of RRF will inevitably predict earlier technique failure. This is perhaps the biggest difficulty in interpreting the second main finding of Liao et al.; we do not know how much of the association between the rate of loss of RRF and technique failure is a consequence of clinician bias in switching patients to HD, in part because RRF has been lost or because it is actually the primary reason for technique failure. Modality switching is complex, and although the primary trigger for the change may have been, for example, peritonitis, the readiness to switch may well be influenced by other factors associated with a more rapid decline in RRF.

One of the strengths of this study is the wide inclusion of other factors thought to be associated with the rate of decline in RRF. Comorbidity, especially diabetes and heart failure, predicted an increased rate of loss, in contrast to the findings of the NECOSAD study [2], whereas in agreement with NECOSAD, episodes of hypotension/dehydration were independently associated with accelerated loss of RRF. It is interesting to note that a higher level of RRF and use of diuretics at the start of treatment were associated with increased rate of loss. One hypothesis that links these observations might be that the rate of loss of RRF is in itself a marker of difficulty in the management of volume status. The patients with pre-dialysis difficulties in volume control would be more likely to start treatment at a higher level of RRF; to be using diuretics, as well as having diabetes or heart failure.

There is increasing evidence that the relationship between fluid status and RRF in PD patients is a two-way street. In addition to the observational data already mentioned, interventional studies designed to alter volume status [10], including two randomized trials [11–13], have shown that change in extra-cellular volume alters urine volume, potentially in both directions [14]. Given these observations, studies of different interventions, such as biocompatible PD solutions on RRF, require careful designing and consideration in their interpretation. In particular, a cross-over study design is problematic when the covariate under analysis is itself changing with time, especially when this rate of change has previously been demonstrated to be non-linear, as is the case with RRF [9]. Several of the studies examining the effects of biocompatible solutions have, however, employed this design (see Table 1), which is satisfactory when looking at dialysate biomarkers or circulating levels of GDP adducts, but less easy to interpret especially when there is also evidence from these studies that these solutions may result in a change in the ultrafiltration capacity of the membrane.

There is no clear message of the effect of the newer biocompatible solutions on membrane function, partially because the solutions are quite variable in their GDP content, the buffer used and in at least one study, multiple solutions are compared using the ‘NEPP’ (NutrinealTM, ExtranealTM and PhysionealTM) regime [15–22]. However, if anything, there tends to be an increase in solute transport and/or a reduction in either the actual amount of achieved ultrafiltration or the ultrafiltration capacity of the membrane, such that the authors report that the net fluid removal in both limbs of the study are identical. None of the studies report fluid status, presumably because none, with the exception of the study from Fan et al. [21] that found no effect, were investigating RRF as a primary outcome variable.

In this context, the BalNet study, published in preliminary form in the Proceedings of the 3rd Asian Chapter of the International Society of Peritoneal Dialysis and in full in this edition of Nephrology Dialysis and Transplantation, is typical of these studies. The strengths of this study are that it avoids a cross-over design, it enrolled incident patients and followed them for a full year. As with all the studies of biocompatible solutions, a significant increase in dialysate CA 125, thought to be a marker of mesothelial integrity and thus reduced membrane injury, was seen. The authors focus on the apparent benefit of the biocompatible fluid in the preservation of RRF, although this could only be demonstrated when applying a secondary form of analysis (mixed
linear modelling adjusting for various baseline factors including age, gender and comorbidity). More convincingly, within-group analysis did show that this fell in the patients using conventional fluids but not the biocompatible fluid. Unfortunately, despite randomization, the membrane function of these two groups does not appear to have been the same. The biocompatible group had higher solute transport throughout the study, and the single most significant difference between the groups was the reduced ultrafiltration achieved in this group (see Table 2 of their article, page XX), a difference that increased during the course of the study despite no change in glucose prescription. In fact, the between-group difference in urine volume at the end of the study was less than the ultrafiltration volume.

What can we conclude from this emerging picture? It is increasingly certain that there is an intimate relationship between fluid management and RRF in PD patients. The new biocompatible solutions may help preserve RRF, but the mechanism is not certain and an inadvertent effect on fluid status seems likely—at least in some of the studies. Future studies of this issue should avoid cross-over design and preferably measure fluid status as well as membrane function. There are, however, more profound questions that need to be addressed. Just because preserved RRF is a marker of better survival in observational cohort studies, this does not tell us that we should do all in our power to preserve RRF, especially if that is at the expense of fluid excess. The apparent beneficial effects of RRF, at least those that relate to better volume management, may simply reflect survival bias. We also need better tools to assess fluid status in PD patients and a better understanding of how fluid status relates to clinical outcomes before any such recommendations can be made.

Conflict of interest statement. The author has conducted studies on fluid management using solutions manufactured by Baxter Healthcare and Gambro.

(See related article by C.-T. Liao et al. Rate of decline of residual renal function is associated with all-cause mortality and technique failure in patients on long-term peritoneal dialysis. *Nephrol Dial Transplant* 2009; 24: 2909–2914.)


References


Received for publication: 13.4.09; Accepted in revised form: 3.6.09