Slouching towards Bethlehem: the beast of biocompatibility

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…And what rough beast, its hour come round at last/
Slouches towards Bethlehem to be born?

William Butler Yeats, 1919

In this issue of Nephrology, Dialysis and Transplantation, Haag-Weber and colleagues report the results of a randomized, multi-centre study comparing the use of a peritoneal dialysis (PD) solution with low levels of glucose degradation products (GDPs) to conventional solutions produced by three major suppliers (Gambrosol, Stay-safe and Dialen)[1]. In contrast to other studies, the patients included in the study had to have a residual glomerular filtration rate (GFR) of >3 mL/min or residual creatinine clearance >6 mL/min. The principal outcomes examined were the rate of decline of residual renal function (RRF) and urine volume over the course of the study, evolution of peritoneal membrane transport characteristics, effluent levels of CA125 as a surrogate for mesothelial cell mass and levels of C-reactive protein (CRP) as a marker for systemic inflammation. The driving hypothesis was that absorbed GDPs and/or their attendant conversion into advanced glycosylation end products (AGEs) are harmful to the kidneys, so that low GDP dialysate should result in less deterioration of kidney function.

The inception cohort had a mean RRF of 6.2–6.7 mL/min and average urine volume close to 1700 mL/24 h. In the patients who completed the study, the percent decline in RRF was −4.3%/month in those on conventional solutions produced by three major suppliers (Gambrosol, Stay-safe and Dialen) compared to −1.5%/month in those on the low-GDP solution, accompanied by a decrease in ultrafiltration rate (GFR) of >3 mL/min or residual creatinine clearance >6 mL/min. The principal outcomes examined were the rate of decline of residual renal function (RRF) and urine volume over the course of the study, evolution of peritoneal membrane transport characteristics, effluent levels of CA125 as a surrogate for mesothelial cell mass and levels of C-reactive protein (CRP) as a marker for systemic inflammation. The driving hypothesis was that absorbed GDPs and/or their attendant conversion into advanced glycosylation end products (AGEs) are harmful to the kidneys, so that low GDP dialysate should result in less deterioration of kidney function.

In the study by Haag-Weber in this issue, the authors concluded that the decreased renal exposure to GDPs in the group using Gambrosol resulted in better preservation of RRF. Furthermore, they proposed that the renoprotective effect may be ultimately responsible for the claim of reduced mortality with the use of these solutions in other reports [2].

This study adds to the growing literature that comforts and buttresses the believers in ‘biocompatible’ solutions, but only further confuses the non-believers and biocompatibility-agnostics. In the last decade, studies have [3–6] or have not [7–11] demonstrated better preservation of RRF, have [4] or mostly have not shown to be associated with lower rates of PD peritonitis, and have [9,10] or have not [5,6,11] been associated with a reduction in blood levels of CRP.

There are many factors that may contribute to the variability in the results, including the composition of the ‘biocompatible’ solution used, which may vary among manufacturers, the amount of overfill in the bag that can confuse the calculation of ultrafiltration and the prevalent rate of peritonitis. In the latter case, centres with low rates of PD peritonitis may be less able to demonstrate a significant drop in the rate with new solutions, compared to centres with more frequent infectious episodes. Similarly, it has been proposed by Haag-Weber and co-authors [1] that studies looking at the effect of newer solutions on RRF are more likely to have a protective effect if the RRF is higher, rather than lower, at the beginning of the study. The only findings that appear to be more or less consistent among the studies are higher levels of CA125 in the dialysate effluent and, paradoxically, an ‘increase’ in membrane transport associated with a concomitant reduction in ultrafiltration [3–5,12].

The biocompatibility–renoprotection hypothesis was the offshoot of the result of a secondary outcome reported in a study of a ‘biocompatible’ solution that was designed primarily to examine the effect of the solution on the peritoneal membrane [3]. The Euro-Balance Trial found a better ‘preservation’ or even resuscitation of RRF when patients were on the new solution in the crossover study. As I have previously noted, there was a change to a more rapid transport status, as measured by D/P creatinine, with the ‘biocompatible’ solution, accompanied by a decrease in ultrafiltration [13]. The subsequent increase in extracellular fluid volume, not the composition of the dialysis fluid, may have been responsible for increased GFR. Indeed, the rapid time course of change in urine volume and its bidirectional nature would be more in keeping with response to extracellular fluid status than kidney damage from absorbed GDPs or production of AGEs [13,14]. In the study by Haag-Weber in this issue, ultrafiltration could not be closely measured, but it is note-
worthy that, as demonstrated in Table 4, the 24-h ultrafiltration (not corrected for overfill) was 446 ± 116 mL/day in the standard fluid group and half as much in the Gambrosol group [1]. The reduced ultrafiltration again suggests the same alternate hypothesis as in the Euro-Balance Study, that is, that a reduction in ultrafiltration with the ‘biocompatible’ solution kept the patients more subclinically fluid-overloaded, which plumped up the RRF [13,14].

Is there a physiological underpinning to the hypothesis that the newer PD solutions lead to less absorption of GDPs, less formation of AGEs, and ultimately less renal damage or even mortality from these compounds? As pointed out previously [13], elevated serum levels of AGEs are seen in chronic kidney disease itself, and the incremental contribution from PD fluids is probably not significant. Serum levels of pentosidine are lower in patients on PD compared to those on haemodialysis [15], and serum AGE peptide levels are the same in patients on both modalities [16]. Carboxymethyllysine (CML) levels in patients on haemodialysis or haemofiltration are as high, or even higher, than those in patients on PD fluids [17]. In a study comparing standard versus low-GDP solutions, plasma levels of CML were similar in both groups and to those in haemodialysis patients [18]. While intravenous infusion of GDPs has been shown to accelerate renal damage in a subtotal nephrectomy model of CKD [19], when 3,4-DGE, a toxic GDP, is infused, the peritoneal cavity, it cannot be detected in the plasma [20]. In summary, there is little evidence to presuppose that the new solutions result in decreased systemic levels of GDPs or AGEs, and in this way better protect RRF.

Finally, despite all the evidence to the contrary, if one takes on faith (as so many do) that the new solutions somehow do protect and prolong RRF, does that translate into improved survival? While there are many studies that show the association of better RRF with improved survival, the mechanism of the association is not clear. Aside from the benefit of the renal contribution to blood purification and salt and water excretion, there is the possibility that it is healthier, relatively non-inflamed patients who maintain their RRF longer. If that is the case, the link between RRF and survival may be because the patient is intrinsically healthier and lives longer for that reason, not because of any contribution from the kidneys. In that case, it would not be expected that prolonging RRF alone would result in any survival advantage.

Haag-Weber and colleagues are to be congratulated on completing a difficult multi-centre study. However, their conclusion that the change in RRF over time is the result of a diminished effect of systemic GDPs and AGEs rests on a shaky, unproven physiologic platform, and the contribution of diminished ultrafiltration and subclinical volume overload remains unexplored. The beast of biocompatibility still struggles to be born.

Conflict of interest statement. None declared.

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