TRIALS (AND TRIBULATIONS) OF BIOCOMPATIBLE PERITONEAL DIALYSIS FLUIDS

A key factor implicated in the local and systemic complications of peritoneal dialysis (PD) is the “unphysiologic” nature of conventional PD fluids, particularly acidic pH (5.0 – 5.8) and high concentrations of glucose degradation products (GDPs) generated as a byproduct of the heat sterilization process (1,2). Acidic PD fluid promotes mesothelial cell damage and neoangiogenesis *in vitro* (3) and infusion pain in the clinical setting (4). Exposure to GDPs also results in reduced growth and viability of peritoneal cell populations (mesothelial cells, fibroblasts, macrophages, and leukocytes), increased collagen deposition, augmented secretion of proinflammatory cytokines such as vascular endothelial growth factor, local production of damaging advanced glycation endproducts (AGEs) (5), and stimulation of epithelial–mesenchymal transition (6–9). The GDPs in standard PD fluids are also known to be absorbed systemically, possibly accelerating loss of residual renal function because of the proinflammatory, proapoptotic, and pro-oxidative effects of AGEs (10).

Concerns about the deleterious effects of conventional PD fluids have led, over the last 15 years, to the development of newer “biocompatible” PD fluids, which have a neutral pH and are low in GDPs (11). These novel solutions have been shown, in both *in vitro* and *in vivo* studies, to largely abrogate most of the adverse effects of conventional solutions on the peritoneal membrane (1,7,12–14). Furthermore, several large observational retrospective cohort studies in Korea have reported that, compared with administration of conventional solutions, administration of neutral-pH low-GDP fluids buffered with either lactate (15,16) or lactate/bicarbonate (17) is associated with improved patient survival—although those findings are potentially limited by confounding by indication (18). A number of small, short-duration randomized controlled trials have demonstrated significant improvements in the effluent biomarkers of peritoneal membrane integrity, but those studies have not identified any benefits with respect to patient or technique survival, and they failed to show consistent effects on other clinically important outcomes, such as peritonitis rates, small-solute clearance, peritoneal ultrafiltration, or decline in residual renal function. Those trials, summarized in Table 1, were limited by inadequate

statistical power, low event rates, high drop-out rates, treatment-associated changes in fluid status, and often, poor methodologic quality, enrolment of prevalent PD patients, and single-center designs.

Recently, our group published the findings of the BALANZ study, an investigator-initiated prospective, open-label, randomized placebo-controlled phase IV trial of neutral-pH lactate-buffered low-GDP fluid (Balance: Fresenius Medical Care, Bad Homburg, Germany) compared with conventional lactate-buffered standard PD solutions (Stay•Safe: Fresenius Medical Care). The 185 patients involved came from 16 centers across Australia, New Zealand, and Singapore (29). The principal findings of the trial were that, compared with administration of conventional fluid, administration of the biocompatible fluid resulted in a significant delay in the onset of anuria, a significant 36% reduction in peritonitis rates, and a numerically slower, though not statistically significant, decline in residual renal function (particularly in the first year). Patients in the biocompatible group also experienced an early rise in peritoneal solute transport rate, accompanied by lower peritoneal ultrafiltration volumes and higher urine volumes. However, the two groups showed no differences with respect to indices of overall fluid status. The trial was not adequately powered to assess technique or patient survival.

In the current issue of *Peritoneal Dialysis International*, Lai *et al.* (30) report the results of a randomized controlled trial, conducted in four Hong Kong centers, in which 125 incident PD patients assigned to receive either biocompatible fluid [Gambrosol Trio: Gambro Lundia AB, Lund, Sweden ($n = 41$); Physioneal 40, Baxter Healthcare Corporation, Deerfield, IL, USA ($n = 12$); Balance ($n = 5$)] or conventional fluid [Dianeal PD-2: Baxter Healthcare Corporation ($n = 43$); ANDY-Disc: Fresenius Medical Care ($n = 24$)] for an average period of 3.6 years. The composite co-primary outcomes of the study were a biochemical profile of 18 cytokines, growth factors, adipokines, and cardiac biomarkers in both serum and dialysate effluent, evaluated at an average period of 2.3 years; and dialysis adequacy [residual glomerular filtration rate (GFR), daily urine output, total and peritoneal Kt/V, total and peritoneal creatinine clearance] evaluated at an average duration of 3.6 years. Compared with controls, patients

TABLE 1
Summary of Published Randomized Controlled Trials of Biocompatible Compared with Standard Peritoneal Dialysis Solutions

Reference	Comparison	Patients (I/P) (n)	Centers (n)	APD (Y/N)	Duration (years)	Allocation conceal- ment	Trial quality			Changes observed				
							ITT (Y/N)	Blind- ing (Y/N)	Drop- out (%)	RRF	Peritoneal clearance	UF	PSTR	Peritonitis
Tranæus, 2000 (19)	Physioneal ^a vs Dianeal ^a	P 106	34	N	0.5	Yes	N	N	17	None	None	↑	None	None (↓ at 1 year)
Le Poole <i>et al.</i> , 2004 (20)	NEPP ^a vs Dianeal	I 63	2	N	0.5	Unclear	N	N	11	None	None	None	↑	None
Williams <i>et al.</i> , 2004 (21)	Balance ^b vs Stay•Safe ^b	P 86	22	N	0.25	Unclear	N	N	17	↑	None	↓	↑	None
Szeto <i>et al.</i> , 2007 (22)	Balance vs Stay•Safe	I 50	1	N	1	Yes	Y	N	2	None	None	None	NA	None
Choi <i>et al.</i> , 2008 (23)	Balance vs Dianeal	P 104	1	N	1	Unclear	N	N	35	None	↑ Kt/V	↑	NA	NA
Fan <i>et al.</i> , 2008 (24)	Physioneal–Balance vs Dianeal–Stay•Safe	I 118	1	Y	1	Unclear	Y	N	21	None	NA	None	None	None
Kim <i>et al.</i> , 2009 (25)	Balance vs CAPD	I 91	5	N	1	Unclear	N	N	24	↑	NA	↓	↑	None
Weiss <i>et al.</i> , 2009 (26)	Bicarbonate vs Stay•Safe	P 53	17	N	0.25	Unclear	N	N	36	↑	NA	↓	None	None
Haag–Weber <i>et al.</i> , 2010 (27)	Gambrosol Trio ^c vs Gambrosol ^c – Stay•Safe–Dianeal	P 80	23	N	1.5	Yes	N	N	51	↑	NA	None	None	None
Srivastava <i>et al.</i> , 2011 (28)	Physioneal–Balance vs Dianeal–Stay•Safe	I 267	1	Y	~2.3	Unclear	Y	N	NS	NA	NA	NA	NA	None
Johnson <i>et al.</i> , 2012 (29)	Balance vs Stay•Safe	I 185	16	Y	2	Yes	Y	N	2	↑	None	↓	↑	↓
Lai <i>et al.</i> , 2012 (30)	Gambrosol Trio–Physioneal–Balance vs Dianeal–ANDY–Disc ^b	I 125	4	N	2.3	Unclear	N	N	0	↑	None	↓	↑	NA

I/P = incident or prevalent; APD = automated peritoneal dialysis; Y/N = yes or no; ITT = intention to treat; RRF = residual renal function; UF = ultrafiltration; PSTR = peritoneal solute transport rate; NEPP = regimen of Nutrineal×1, Extraneal×1, Physioneal×2; NA = not assessed; CAPD = continuous ambulatory peritoneal dialysis; NS = not specified.

^a Baxter Healthcare Corporation, Deerfield, IL, USA.

^b Fresenius Medical Care, Bad Homburg, Germany.

^c Gambro Lundia AB, Lund, Sweden.

receiving biocompatible fluids had significantly lower effluent levels of resistin, interleukin-1, and interleukin-8, but higher levels of adiponectin and transforming growth factor β . Patients in the biocompatible group had higher serum levels of adiponectin and lower serum levels of leptin, tumour necrosis factor α , and neutrophil gelatinase-associated lipocalin. With respect to dialysis adequacy, patients receiving biocompatible fluids had higher urine output and slower decline of both urine output and GFR. The peritoneal solute transport rate was increased in the biocompatible group starting at 1 month, accompanied by a decrease in peritoneal ultrafiltration. No differences between the groups were observed with respect to total or peritoneal small-solute clearances, cardiovascular event-free survival (timed from dialysis commencement), or patient survival (timed from the dialysate and serum sample collections, at an average period of 2.3 years after dialysis commencement). No information was provided on peritonitis rates. The authors concluded that low-GDP biocompatible fluid resulted in an improvement in local peritoneal homeostasis by ameliorating peritoneal inflammation.

Lai *et al.* are to be congratulated for completing one of the largest multicenter randomized controlled trials of biocompatible PD fluids, with the longest follow-up, to date. Unfortunately, the unorthodox trial design significantly limits the conclusions that can be drawn from the study.

The authors describe a process of “simple randomization” made by the patient’s training officer at each individual renal center, but not the method used to generate the random allocation sequence, whether randomization was stratified for center (to exclude the possibility of “center effects” confounding study outcomes), and whether any steps were taken to conceal the sequence until interventions were assigned. It is also not clear that this study followed an intention-to-treat design, because patients had to survive and remain on PD from the time of dialysis commencement until the census date when serum and dialysate samples were collected (an average of 2.3 years later). It is likely that other patients dropped out beforehand (for example, because of death or hemodialysis transfer), thereby potentially leading to informative censoring bias if such drop-outs were related to treatment assignment. To help gauge the study’s generalizability to PD populations, it would have also been important to know how many patients from all four centers were excluded from the study.

The open-label design of the trial may also have led to co-intervention bias. As a matter of concern, patients were not informed of the study at the time that their

PD fluids were assigned; informed consent appears to have been obtained at the time of serum and effluent collection. Survival was timed from that variable sample collection date rather than from randomization. The large number of endpoints chosen for the composite co-primary endpoints (42 in total) greatly increased the probability of a type 1 statistical error—that is, the finding of a statistically significant difference because of chance alone. The chosen endpoints represent mostly surrogate rather than patient-level outcomes and variably changed in directions that were potentially beneficial (for example, reduced dialysate concentrations of interleukins 1 and 8), neutral (most parameters), or deleterious (for example, increased dialysate transforming growth factor β), thereby making it difficult to evaluate the overall benefit of biocompatible fluid administration. The census sampling occurred at a single variable time point after randomization (2.2 ± 0.2 years in the biocompatible group compared with 2.4 ± 0.18 years in the control group) leading to possible lead-time bias in the evaluation of biochemistry profiles and the subsequent survival analyses. No adjustment was made for baseline values (for example, by analysis of covariance), serial studies were not performed, and it was not clear whether the samples were batched or analyzed at a central or local laboratory.

The use of a variety of biocompatible fluids from 3 different commercial providers in the intervention arm was potentially problematic because the GDP concentrations vary considerably between those solutions (3,27,31,32). The 4-hour ultrafiltration volumes were similar between the groups, and yet the 24-hour ultrafiltration volumes were lower in the biocompatible group, suggesting different peritoneal glucose exposures between the groups. However, no information was provided about peritoneal glucose exposure, icodextrin use, or fluid status assessment (although levels of brain natriuretic peptide were somewhat higher in the biocompatible fluid arm). Similarly, information was not provided about prescription of medications such as angiotensin converting-enzyme inhibitors and diuretics, which may have influenced the residual GFR and urine volume outcomes in the study.

What, then, can we conclude from the study of Lai *et al.*, taken in the context of all randomized trials of neutral-pH low-GDP “biocompatible” fluids that have preceded it? First, consistent changes in dialysate effluent markers of peritoneal integrity and inflammation appear to be demonstrated with the administration of biocompatible fluids, although the clinical significance of those changes remains uncertain. Second, there is clinical evidence that neutral-pH low-GDP fluids reduce infusion pain in PD patients (4). Third, biocompatible fluids

exert either neutral or beneficial effects on residual renal function, dialytic small-solute clearance, peritonitis rates, and systemic inflammatory markers in short- to medium-term investigations. Fourth, the effects of biocompatible fluids on technique and patient survival are unknown, because no adequately powered trials have been performed to date. Our group is attempting—through a meta-analysis of all randomized controlled trials—to further clarify whether biocompatible fluids offer important clinical benefits (33).

Given that the overall results of available clinical trials of biocompatible fluids relative to standard solutions are either neutral or beneficial and not harmful, the use of biocompatible fluids in clinical practice becomes a matter for clinicians, who should weigh the quality and quantity of clinical safety and efficacy evidence against a consideration of the additional cost. We believe it likely that the prescription of biocompatible fluids will increase over time, which will in turn lead to a reduction in cost and further increased uptake. In much the same way that hemodialysis practice evolved from acetate to bicarbonate dialysates on the basis of not particularly strong clinical trial evidence and prices that approached parity over time (34), we can envisage a scenario in the medium-term future in which PD practice may well evolve from acidic high-GDP fluids to neutral-pH low-GDP solutions. Such an evolution in PD clinical practice would be greatly facilitated by the global PD research community collaborating to a much greater extent than it currently does to conduct large, adequately powered, multicenter and multi-country randomized controlled trials addressing promising interventions (such as biocompatible fluids) that have the potential to positively influence patient-level outcomes. The development of a global PD clinical research network would also help to facilitate much-needed improvements in the quality of clinical trials currently being performed in PD.

The deepest sin against the human mind is to believe things without evidence.

— Thomas Huxley

DISCLOSURES

DWJ is a consultant for Baxter Healthcare Pty Ltd. and has previously received research funds from that company. He has also received speakers' honoraria and research grants from Fresenius Medical Care. He has previously been a consultant to Gambro Pty Ltd. He is a Councillor of the International Society for Peritoneal Dialysis and a current recipient of a Queensland Government Health Research Fellowship. FGB is a consultant for

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REFERENCES

1. Topley N. *In vitro* biocompatibility of bicarbonate-based peritoneal dialysis solutions. *Perit Dial Int* 1997; 17:42–7.
2. Witowski J, Jörres A, Korybalska K, Ksiazek K, Wisniewska-Elnur J, Bender TO, *et al.* Glucose degradation products in peritoneal dialysis fluids: do they harm? *Kidney Int Suppl* 2003; (84):S148–51.
3. Hoff CM. *In vitro* biocompatibility performance of Physioneal. *Kidney Int Suppl* 2003; (88):S57–74.
4. Mactier RA, Sprosen TS, Gokal R, Williams PF, Lindbergh M, Naik RB, *et al.* Bicarbonate and bicarbonate/lactate peritoneal dialysis solutions for the treatment of infusion pain. *Kidney Int* 1998; 53:1061–7.
5. Krediet RT, Zweers MM, van der Wal AC, Struijk DG. Neoangiogenesis in the peritoneal membrane. *Perit Dial Int* 2000; 20(Suppl 2):S19–25.
6. Schambye HT. Effect of different buffers on the biocompatibility of CAPD solutions. *Perit Dial Int* 1996; 16(Suppl 1):S130–6.
7. Witowski J, Jörres A. Effects of peritoneal dialysis solutions on the peritoneal membrane: clinical consequences. *Perit Dial Int* 2005; 25(Suppl 3):S31–4.
8. Nau B, Schmitt CP, Almeida M, Arbeiter K, Ardissino G, Bonzel KE, *et al.* BIOKID: randomized controlled trial comparing bicarbonate and lactate buffer in biocompatible peritoneal dialysis solutions in children [ISRCTN81137991]. *BMC Nephrol* 2004; 5:14.
9. Oh EJ, Ryu HM, Choi SY, Yook JM, Kim CD, Park SH, *et al.* Impact of low glucose degradation product bicarbonate/lactate-buffered dialysis solution on the epithelial-mesenchymal transition of peritoneum. *Am J Nephrol* 2010; 31:58–67.
10. Justo P, Sanz AB, Egido J, Ortiz A. 3,4-Dideoxyglucosone-3-ene induces apoptosis in renal tubular epithelial cells. *Diabetes* 2005; 54:2424–9.

11. McIntyre CW. Update on peritoneal dialysis solutions. *Kidney Int* 2007; 71:486–90.
12. Mortier S, Faict D, Schalkwijk CG, Lameire NH, De Vriese AS. Long-term exposure to new peritoneal dialysis solutions: effects on the peritoneal membrane. *Kidney Int* 2004; 66:1257–65.
13. Mortier S, Faict D, Lameire NH, De Vriese AS. Benefits of switching from a conventional to a low-GDP bicarbonate/lactate-buffered dialysis solution in a rat model. *Kidney Int* 2005; 67:1559–65.
14. Mackenzie R, Holmes CJ, Jones S, Williams JD, Topley N. Clinical indices of *in vivo* biocompatibility: the role of *ex vivo* cell function studies and effluent markers in peritoneal dialysis patients. *Kidney Int Suppl* 2003; (88):S84–93.
15. Lee HY, Park HC, Seo BJ, Do JY, Yun SR, Song HY, *et al.* Superior patient survival for continuous ambulatory peritoneal dialysis patients treated with a peritoneal dialysis fluid with neutral pH and low glucose degradation product concentration (Balance). *Perit Dial Int* 2005; 25:248–55.
16. Lee HY, Choi HY, Park HC, Seo BJ, Do JY, Yun SR, *et al.* Changing prescribing practice in CAPD patients in Korea: increased utilization of low GDP solutions improves patient outcome. *Nephrol Dial Transplant* 2006; 21:2893–9.
17. Han SH, Ahn SV, Yun JY, Tranæus A, Han DS. Mortality and technique failure in peritoneal dialysis patients using advanced peritoneal dialysis solutions. *Am J Kidney Dis* 2009; 54:711–20.
18. Johnson DW, Williams JD. Impact of peritoneal dialysis solutions on outcomes. In: Molony DA, Craig JC, eds. *Evidence-Based Nephrology*. Oxford, UK: Blackwell; 2009.
19. Tranæus A. A long-term study of a bicarbonate/lactate-based peritoneal dialysis solution—clinical benefits. The Bicarbonate/Lactate Study Group. *Perit Dial Int* 2000; 20:516–23.
20. le Poole CY, van Ittersum FJ, Weijmer MC, Valentijn RM, ter Wee PM. Clinical effects of a peritoneal dialysis regimen low in glucose in new peritoneal dialysis patients: a randomized crossover study. *Adv Perit Dial* 2004; 20:170–6.
21. Williams JD, Topley N, Craig KJ, Mackenzie RK, Pischetsrieder M, Lage C, *et al.* on behalf of the Euro Balance Trial Group. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (Balance) on the peritoneal membrane. *Kidney Int* 2004; 66:408–18.
22. Szeto CC, Chow KM, Lam CW, Leung CB, Kwan BC, Chung KY, *et al.* Clinical biocompatibility of a neutral peritoneal dialysis solution with minimal glucose-degradation products—a 1-year randomized control trial. *Nephrol Dial Transplant* 2007; 22:552–9.
23. Choi HY, Kim DK, Lee TH, Moon SJ, Han SH, Lee JE, *et al.* The clinical usefulness of peritoneal dialysis fluids with neutral pH and low glucose degradation product concentration: an open randomized prospective trial. *Perit Dial Int* 2008; 28:174–82.
24. Fan SL, Pile T, Punzalan S, Raftery MJ, Yaqoob MM. Randomized controlled study of biocompatible peritoneal dialysis solutions: effect on residual renal function. *Kidney Int* 2008; 73:200–6.
25. Kim S, Oh J, Kim S, Chung W, Ahn C, Kim SG, *et al.* Benefits of biocompatible PD fluid for preservation of residual renal function in incident CAPD patients: a 1-year study. *Nephrol Dial Transplant* 2009; 24:2899–908.
26. Weiss L, Stegmayr B, Malmsten G, Tejde M, Hadimeri H, Siegert CE, *et al.* Biocompatibility and tolerability of a purely bicarbonate-buffered peritoneal dialysis solution. *Perit Dial Int* 2009; 29:647–55.
27. Haag-Weber M, Krämer R, Haake R, Islam MS, Prischl F, Haug U, *et al.* on behalf of the DIUREST Study Group. Low-GDP fluid (Gambrosol Trio) attenuates decline of residual renal function in PD patients: a prospective randomized study. *Nephrol Dial Transplant* 2010; 25:2288–96.
28. Srivastava S, Hildebrand S, Fan SL. Long-term follow-up of patients randomized to biocompatible or conventional peritoneal dialysis solutions show no difference in peritonitis or technique survival. *Kidney Int* 2011; 80:986–91.
29. Johnson DW, Brown FG, Clarke M, Boudville N, Elias TJ, Foo MW, *et al.* on behalf of the BaLANZ Trial Investigators. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. *J Am Soc Nephrol* 2012; :[Epub ahead of print].
30. Lai KN, Lam MF, Leung JCK, Chan LY, Lam CWK, Chan IHS, *et al.* A study of the clinical and biochemical profile of peritoneal dialysis fluid low in glucose degradation products. *Perit Dial Int* 2012; 31:280–291.
31. Johnson DW, Clarke M, Wilson V, Woods F, Brown FG. Rationale and design of the BaLANZ trial: a randomised controlled trial of low GDP, neutral pH versus standard peritoneal dialysis solution for the preservation of residual renal function. *BMC Nephrol* 2010; 11:25.
32. Himmele R, Jensen L, Fenn D, Ho CH, Sawin DA, Diaz-Buxo JA. A new neutral-pH low-GDP peritoneal dialysis fluid. *Perit Dial Int* 2012; :[Epub ahead of print].
33. Wiggins KJ, Craig JC, Johnson DW, Strippoli GFM. Biocompatible dialysis fluids for peritoneal dialysis. *Cochrane Database Syst Rev* 2009; :CD007554.
34. MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al.* Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews. *Health Technol Assess* 1998; 2:1–166.