Biocompatible Solutions and Long-Term Changes in Peritoneal Solute Transport

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**Abstract**

**Background and objectives**

The inflammation-driven increase in peritoneal solute transport rate (PSTR) that occurs during long-term peritoneal dialysis (PD) is associated with higher mortality, hospitalization and encapsulating peritoneal sclerosis. As biocompatible solutions were developed to mitigate these effects, we examined the association with their use and longitudinal PSTR.

**Design, setting, participants, and measurements**

We analysed subjects from the multinational prospective Global Fluid Study with ≥three PSTR measurements more than two months from the start of PD. Follow up was for 7.5 years (median of 2.3 IQR 1.8-3.6) in biocompatible solutions and 12.8 years (median 3.2 IQR 1.9-4.3) for standard solutions. Using a random intercept/slopes multilevel model we examined the association of patients using biocompatible solutions and PSTR over time adjusting for centre effects, dialysate dextrose concentration, baseline dialysate interleukin-6 concentration, icodextrin use, residual kidney function and peritonitis.

**Results**

Of 366 patients, the 71 receiving biocompatible solutions throughout their time on PD had a mean adjusted dialysate to plasma creatinine ratio (D/P CR) of 0.67, compared to 0.72 for standard solutions (p=0.02). With duration of treatment there was a continuous increase in PSTR in patients using standard solutions (range 2 months to 4 years). In contrast, patients using biocompatible solutions PSTR plateaued after two years of therapy. These changes in PSTR were independent from baseline inflammation and of time varying predictors of faster PSTR. In patients suffering episodes of peritonitis whilst using standard solutions, there was an associated increase in PSTR of 0.033 (95% CI 0.015, 0.052) per episode, whereas in patients using biocompatible solutions there was no change in this parameter (-0.014, 95% CI -0.033, 0.003).

**Conclusions**

 These data suggest a different temporal pattern in changes in PSTR occur during the course of PD according to solution type and that patients using biocompatible solutions avoid the increase in solute transport associated with peritonitis.

**Introduction**

Over time peritoneal dialysis (PD) can cause progressive injury to the peritoneal membrane. Local inflammation, with an increase in membrane vascularity, is the likely driver of this, evidenced by faster peritoneal solute transport rate (PSTR).1,2 Faster PSTR is strongly associated with the likelihood of poor outcomes including technique failure and mortality. 3 Encapsulating peritoneal sclerosis is a rare but serious complication also associated with higher PSTR.4 Mechanisms leading to this increase are multifactorial but may include conventional (bioincompatible) dialysis solutions, cumulative glucose (or glucose degradation product) exposure and episodic peritonitis.5

Animal model data suggests that biocompatible solutions are better able to preserve membrane integrity *in vivo* after exposure to PD solutions6 and data on peritoneal morphology suggests fewer adverse changes with biocompatible solutions .7 an early cross-over study in patients suggested that biocompatible solutions may increase PSTR,8 but more recent meta-analyses 9,10 have failed to demonstrate a consistent effect. As shown in the Balance in Australia and New Zealand peritoneal dialysis patients BalANZ® study, 11 differences may vary over time, however the greatest clinical concern is over long-term changes in PSTR, which no randomised trials have directly addressed.

In the present study we undertook the first longitudinal analysis of the global fluid study cohort to test the hypothesis that biocompatible solutions reduces long term rises in PSTR, leading to stable PSTR over longer periods on PD.

**Methods**

*Study design*

The Global Fluid Study was an international multi-centre prospective observational cohort study, detailed by Lambie *et al*.12 The study included 10 centres from the UK, Canada and South Korea enrolling patients from June 2002 to December 2008, censored at centre specific dates during December 2010. Any patient on PD capable of informed consent was eligible.

Data was collected on a purpose-built access database (PDDB). Ethical approval was obtained from the multi-centre research ethics committee for Wales, from Kyungpook National University Hospital ethics committee and from University of Alberta ethics committee. The study adhered to the Declaration of Helsinki. Written informed consent was obtained from all patients.

Comorbidity data utilised the validated Stoke Comorbidity Index13. Data collected on PD regime included type of PD, use of icodextrin, brand of solution and dose. PSTR was measured as the 4-hour dialysate/plasma creatinine ratio with 2.5% or 4.25% dextrose approximately every 6 months. Daily dialysate dextrose concentration was calculated as the average of the dextrose concentrations in all bags used in a 24-hour period e.g. a regime of 2 bags of 2 liters at 1.5% dextrose, one bag of 2 liters at 2.5% dextrose, and one bag of 1.5 liters of 7.5% icodextrin has a daily dialysate dextrose concentration = (4x1.5 + 2x2.5 + 1.5x0)/8 = 1.38%).

Dialysate and plasma samples were taken during routine clinical testing, stored locally at -80°c and transferred to a central laboratory (Cardiff, UK). Electrochemiluminescence immune assays for Interleukin-6 IL-6 levels used the commercially available pro-inflammatory i 4-plex (meso-scale discovery, Gaithersburg, Maryland, USA). Baseline dialysate and peritoneal IL-6 were used for this analysis, log transformed due to their log-normal distribution.

Patients were included if they had had three or more PSTR measurements beyond the first 2 months on PD, with the first measurement less than twelve months from the start of PD, and remained on either biocompatible solutions or standard solutions during follow up. Measurements over 7 years after the start of PD were removed due to low patient numbers and no biocompatible solutions patients having measurements past 7 years. 2 centres were not included as one lacked longitudinal follow up data and another did not use biocompatible solutions

*Statistical analysis*

A multi-level model with an unstructured covariance matrix was used to assess patterns of PSTR over time. Biocompatible solutions usage and the main effect of time were forced in, and a quadratic term for time retained as highly significant. Centre, icodextrin use, average dextrose exposure, dialysate and plasma IL-6 levels, urine volume, peritonitis count, age, gender, CAPD or APD and comorbidity score and their interactions with time were tested for with backwards selection. Dialysate and plasma IL-6 were transformed to log10 due to the log-normal distribution. A random intercept at patient level and random slopes for linear and quadratic time variables were significant and between person variance over time was determined from these. Homoskedasticity and level 2 normality assumptions were tested. Marginal plots were used for adjusted PSTR results. AIC and BIC were used to assess dialysate glucose measures in a sensitivity analysis.

Cox proportional hazards models adjusted for centre, dextrose exposure, icodextrin and dialysate IL-6 were tested for proportionality with log-log plots. Missing data, ranging from 0% to 5% for different variables, were considered missing at random and complete case analysis used all analyses used stataIC version12 (college station, tx), with runmlwin for the multi-level model in MLwiN (v2.31).

**Results**

*Patient characteristics*

366 patients with 2290 measurements were included in the final analysis (Figure 1). Of the 71 patients in the biocompatible solutions -only group, 58 (82%) used Baxter Physioneal, 8 (11%) used Fresenius Staysafe® balance and 5 (7%) used Gambrosol-Trio. Of the 295 patients in the standard solutions-only group, 245 used Baxter Dianeal, 50 used Fresenius Staysafe® and one used Boryung Peresis. Patients using biocompatible solutions were less likely to be on APD and had a shorter duration on PD due to the small number of prevalent patients using biocompatible solutions. (Table 1). Follow up was for 7.5 years (median of 2.3 IQR 1.8-3.6) in biocompatible solutions and 12.8 years (median 3.2 IQR 1.9-4.3) for standard solutions. There was no apparent difference in time to treatment failure between biocompatible solutions and standard solutions (cox proportional hazards regression hr 1.18, 95% CI 0.67 to 2.06). Drop-out caused by death, transplantation or treatment failure in the biocompatible solutions and standard groups were 50% (n=25) and 61% (n=138) respectively after 3.5 years. 124 patients recorded using both biocompatible solutions and standard solutions at different time points were not included in the analysis. Baseline characteristics in this group compared to patients included in the final analysis were not clinically significantly different for age, gender comorbidity score and urine volume but were clinically significantly different with regards to time on PD and modality of PD. (Table 1)

*Peritoneal transport over time*

The adjusted PSTR two months after the start of PD was higher in standard solutions (0.721) compared with biocompatible solutions (0.622). With standard solutions, PSTR remains approximately level until an increase between 3.5 (0.721) and 7 years (0.741) of treatment (Figure 2) when adjusted for other known determinants of PSTR. With biocompatible solutions, PSTR was lower at baseline with a steeper initial rise in PSTR. By two years therapy PSTR was similar for both solutions (adjusted PSTR standard solutions 0.724 95% CI 0.709 to 0.738, biocompatible solutions 0.722 (95% CI 0.689 to 0.751). There was, however, no further increase in PSTR in patients using biocompatible solutions between years 2 and 4 of treatment. Supplementary Figure 1 shows adjusted change over time overlying individual changes over time.

Including measurements from the start of PD rather than 2 months after the start made no apparent difference (Supplementary Table 2). Both linear and quadratic time functions were included to allow non-linear changes, and these, as well as random effects for them (allowing the trajectory to vary between individuals in a non-linear way) remained significant within the model. (Table 2) A sensitivity analysis retaining all variables without backwards selection made little difference (Supplementary Table 5).

*Dialysate IL-6*

Higher baseline dialysate IL-6 concentrations were associated with a faster PSTR for the duration of follow up (Table 2). Plasma IL-6 levels had no significant association with PSTR (change in PSTR with one log10 increase in plasma IL-6 concentration =0.009, 95% CI -0.049 to 0.069).

*Peritoneal fluid dextrose and icodextrin*

The median peritoneal daily dextrose concentration increased with time, from 1.5% (IQR 1.38-1.88) dextrose at one year to 1.74% (IQR 1.38-2.19) dextrose at six years. Icodextrin use also increased with PD duration (31% of patients in the first 6 months rising to 55% after 3.5 years) and it was associated with a faster solute transport in the fully adjusted multilevel model (table 2).

In the fully adjusted model, icodextrin use had no association with the trajectory of PSTR over time, but the daily dextrose concentration did (Figure 3), with little difference in PSTR at the start and increasing difference with duration of PD. A 1.93% daily dextrose concentration (75th centile, “high glucose”) had an adjusted PSTR of 0.727 (95% CI 0.712 to 0.741) at 2 years and 0.811 (95% CI 0.775 to 0.846) after 6 years on PD. A 1.33% daily dextrose concentration (25th centile, “low glucose”) had an adjusted PSTR of 0.720 (95% CI 0.705 to 0.736) at 2 years and 0.713 (95% CI 0.676 to 0.749) at 6 years.

Sensitivity analysis included substituting daily mass of dextrose (g/day) for daily dextrose concentration resulted in a worse fit for the model (AIC -335.9 and -333.5, BIC -3186.7 and -3174.4 for concentration and mass respectively, more negative values representing an improved fit). Biocompatible solution usage had similar effects on PSTR in patients not using Icodextrin (Supplementary Table 3). There was no interaction between Icodextrin usage and biocompatible solutions usage.

*Residual kidney function*

A larger urine volume was associated with a higher PSTR (table 2). Urine volume reduced with time on therapy, with the median volume at one year being 775ml (interquartile range 270-1223) and 375 ml (interquartile range 0-1160) at six years. Neither kidney Kt/V nor mean urea/creatinine kidney clearance were associated with PSTR when substituted for urine volume (increase in PSTR: per unit of kidney Kt/V =0.001, 95% CI -0.010 to 0.012, per unit of kidney clearance =0.0001, 95% CI -0.0001 to 0.0004). There was no significant interaction with biocompatibility. Biocompatible solutions use was not associated with urine volume in a separate multilevel model (biocompatible solutions coefficient 120 95% CI -39 to 280).

*Peritonitis*

One or more episodes of peritonitis occurred in 198 of the patients studied, 29 biocompatible solutions (41%) and 169 standard solutions (57%). The most common organism in both groups was coagulase negative staphylococcus (biocompatible solutions 24% standard solutions 28%), and culture negative peritonitis/no organism reported was seen in 31% and 38% (biocompatible solutions and standard solutions respectively). A post peritonitis rise in PSTR was seen in standard solutions with no significant effect of peritonitis on PSTR in biocompatible solutions (table 2). In a Cox model there was no difference in time to first peritonitis episode between biocompatible and standard solutions, when adjusted for centre, glucose exposure, icodextrin and dialysate IL-6 (HR 1.54 95% CI 0.94 to 2.52). There were no significant differences in outcome of 1st peritonitis episode between groups (Supplementary Table 4).

*Effect of time varying covariates*

Measures of peritonitis, urine volume and daily dialysate dextrose concentration deteriorate over time, explaining a lot of the measured change in PSTR as illustrated by the small change in the adjusted models (Figures 2 and 3). If these time varying covariates are not adjusted for, the change in PSTR is far greater (Figure 4).

*Changes in variance over time*

Examination of both the spaghetti plots and the covariance of the random effects suggested that the variance in PSTR decreased with time on PD i.e. higher initial measurements are associated with a subsequent fall, and vice versa. Avoiding problems with regression to the mean, the person-level variance was plotted against duration of PD (Figure 5), confirming a fall in variance with time. Most of this decrease is accounted for by the covariates included i.e. dialysate dextrose concentration, dialysate IL-6, use of icodextrin, urine volume and use of standard solutions/ biocompatible solutions (compare line 4 with line 1, Figure 5).

**Discussion**

In the primary longitudinal analysis of this large multi-national cohort study, we tested the hypothesis that biocompatible solutions use would be associated with stable short to medium term membrane function. This hypothesis proved false as PSTR, although starting slower in patients using biocompatible solutions, rises to similar levels seen in standard solutions after two years treatment. After 2 years, there was a potentially beneficial effect of biocompatible solutions on PSTR, with abrogation of the increases in PSTR observed in patients using standard solutions. In addition, the increases in PSTR associated with peritonitis episodes were absent in patients using biocompatible solutions. The magnitude of these effects was less than the impact of using higher dialysate dextrose concentrations.

For standard solutions, when adjusted for peritonitis, daily glucose exposure and urine volume, there was no evidence of an increase in PSTR over the first two years of treatment. This finding contrasts with previous studies finding either a reduction in PSTR between one and four months of treatment, 14 or a significant increase in PSTR between one month and six months in patients. 1 two explanations can potentially resolve these apparently contradictory observations. Firstly, there may well be differences in the definition of PD start date and in the exact timing of the first peritoneal equilibration test, a period with rapid changes in PSTR.15 indeed, we found significant between-patient variability during the first year of PD, visible on the spaghetti plots with the PSTR falling during the early period in some patients and rising in others. Secondly, there is a significant effect of dialysate glucose, residual kidney function and a cumulative effect of peritonitis, all of which can change with time and have been adjusted for in our analysis. Therefore, the different conclusions in the previous studies could be due to differences in the definition of PD start date, unmeasured determinants of the early variability in solute transport and variation in peritonitis, residual kidney function and dialysate dextrose concentration.

The unadjusted model showed a clear overall increase in PSTR over time (Supplementary Table 1), mostly accounted for by peritonitis, glucose exposure and residual kidney function. This finding is in keeping with previous cohort studies describing membrane injury, explained by changes in peritonitis, glucose exposure and residual kidney function. 1,3,16,17

As found previously 17,18 these results show that increasing daily glucose exposure is associated with long-term increases in PSTR. This could be a result of glucose-driven pathophysiological changes in the membrane and/or this could be a treatment response to increasing membrane permeability driven by other clinical factors e.g. peritonitis.

The largest randomised study examining the effect of biocompatible solutions on membrane function is the balANZ study, demonstrating that initial PSTR was faster with biocompatible solutions compared to standard solutions. Over two years the PSTR remained stable in biocompatible solutions treated patients whereas it increased in patients treated with standard solutions.11 in contrast, in this observational cohort we found a slower PSTR in biocompatible solutions at the beginning of therapy but differences disappeared after two years treatment. Between two to four years of treatment, average PSTR remained stable in the biocompatible solutions group but increased in the standard solutions group. One possible explanation for these observed differences could be differences in the manufacturer/composition of solutions used. Although the electrolytes in most solutions are similar, they are manufactured differently, contain different buffers, have different pH values and are reported to have different levels of glucose degradation products. This study, although based on larger numbers with longer spells on PD, contained three different brands of biocompatible solutions, with the majority on Physioneal using a bicarbonate/lactate buffer. BalANZ exclusively used the lactate-buffered balance with a pH of 7.0. Unfortunately, we did not have sufficient numbers using the different manufacturers solutions for a meaningful comparison. Although the data may be viewed as inconsistent, taken together these studies unequivocally demonstrate differences in PSTR changes in patients using standard and biocompatible solutions. Whilst the impact of these differences on clinical outcome remain to be robustly determined, stabilisation of solute transport would generally be regarded as clinically beneficial. 19,20

We observed that patients using icodextrin had an overall faster PSTR which may be the result of indication bias. As opposed to dialysate glucose, there was no deterioration over time in PSTR with icodextrin.

In keeping with previous research demonstrating a robust association between intra-peritoneal interleukin 6 (IL-6) production and faster PSTR, 12,21,22 baseline dialysate IL-6 levels were associated with faster PSTR for the duration of follow up, whilst plasma IL-6 had no effect. Whilst IL-6 has many immunomodulatory effects 23,24 recent observations linking IL-6 signalling to peritoneal VEGF production provide a mechanism by which IL-6, not itself vasoactive, might alter angiogenesis and vascular permeability in the peritoneal membrane. 25

Baseline urine volume has previously been associated with a faster solute transport, 26 a finding replicated in this analysis although with only weak to moderate evidence. As there was no association in this study between PSTR and kidney Kt/V or clearance the association with urine volume is more likely to be related to fluid balance than clearance *per se*.

Long-term rises in PSTR occur in patients with severe peritonitis or clusters of peritonitis episodes, 1 and the increased power of this study extended this, showing a small but measurable long-term rise in PSTR after a single episode for patients on standard solutions. This is consistent with another report suggesting that the first episode of peritonitis results in PSTR changes. 27

Whilst we did find a significant change in solute transport over time with biocompatible solutions, the association between peritonitis and a faster PSTR disappeared in patients using biocompatible solutions. One potential explanation for this protective effect could be reduced severity of peritonitis with biocompatible solutions, as suggested in the BalANZ study. 16

The strengths of the current study lie in the large size ensuring adequate power, good generalisability with different centres in different countries and the robust and validated statistical approach. The limitations of our analysis include the observational nature of the study, meaning that causality cannot be proven although there were few clinically significant differences between the two patient groups with extensive adjustment for potential confounders. As with all PD studies, informative censoring is a potential issue with non-random dropout of patients. We used an ‘as treated analysis’, excluding patients who switched between standard and biocompatible solutions, limiting the generalisability of the results although there were few significant differences in baseline characteristics between those included and excluded. We did not have sufficient data within the first two months of PD to adequately model the rapid changes known to occur in this period. The biocompatible solutions group as a smaller cohort had a lower number of peritonitis episodes compared to standard solutions but the estimated effects had narrow confidence intervals. There were too few patients to test whether effects differed by manufacturer.

In conclusion, the use of biocompatible solutions (in this case irrespective of manufacturer) was associated with alterations in solute transport rates at different phases of PD treatment. Initially slower and then equivalent at two years biocompatible solutions then have a stable PSTR between 2 and 4 years. These findings add weight to the notion that biocompatible solutions may have long-term clinical benefits although appropriately powered studies will be required to definitively show this is associated with improved outcomes.

**Disclosures**

EE, LT, JC, Y-LK, J-YD, H-BL, SD, NT, SJD and ML have no conflicts to declare.

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**Tables and Figures**

*Table 1. Baseline characteristics for patients using biocompatible or standard solutions. Characteristics for patients excluded as using both biocompatible and standard solutions included in Supplementary Table 1*

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Biocompatible solutions (n=71)** | **Standard solutions (n=295)** |
| **Measures per person** | 6.4 (0.45) | 7.3 (0.21) |
| **Time to end of PD (years)** | 2.6 (2.0-3.9) | 3.5 (2.2-4.8) |
| **Time to first measure (years)** | 0.52 (0.28-0.64) | 0.53 (0.41-0.62) |
| **Baseline measurements for fixed covariates** | **Age (years)** | 55 (14) | 54 (15) |
| **Male Gender** | 50% | 59% |
| **Comorbidity score****(low/medium/high)** | 48%/46%/6% | 40%/52%/8% |
| **Dialysate IL-6 (log transformed pg/ml)** | 4.8 (1.8-12.9) | 4.5 (1.5-10.8) |
| **Plasma IL-6(log transformed pg/ml)** | 1.3 (0.64-2.4) | 1.3 (0.7-2.5) |
| **APD usage compared to CAPD usage** | 6% | 28% |
| **Country****(Canada/UK/Korea)** | 1/35/35 | 16/163/116 |
| **Weight (kg)** | 63 (55-76) | 67 (58 – 77) |
| **Baseline measurements for time varying covariates** | **Average Dialysate Dextrose concentration(g/L)** | 15.0 (15.0-18.7)  | 15.0 (15.0 – 20.1)  |
| **Urine Volume (Litres)** | 0.96 (0.55-1.52) | 0.86 (0.4-1.4) |
| **Icodextrin use** | 29% | 33% |
| **Peritonitis Count (number of episodes per year)** | 0 (0-0.59) | 0.23 (0-0.47) |

Baseline measurements demonstrated using mean with standard deviation or median with interquartile range

*Table 2. Predictors of changes in solute transport over time*

|  |  |  |
| --- | --- | --- |
| **PSTR**  | **Coefficient (95% confidence intervals)** | **p Value** |
| **Difference between Biocompatible and Standard solutions at Start of PD** | -0.049 (-0.091 to -0.008) | 0.02 |
| **Effect of Time with Standard Solutions (years)** | Linear coeff -0.028 (-0.044 to -0.010)Quadratic coeff 0.0009 (-0.0014 to 0.0032) |  0.001\* |
| **Effect of Time with Biocompatible Solutions** | Linear coeff 0.061 (0.026 to 0.095)Quadratic coeff -0.010 (-0.017 to -0.0026) |  0.003\* |
| **Centre effect** | -0.13 to 0.001 | 0.02 |
| **Icodextrin use** | 0.045 (0.030 to 0.060) | <0.001 |
| **Average dextrose concentration in 24 hours (%)** | -0.022 (-0.045 to 0.0005) | 0.06 |
| **Average dextrose concentration with time interaction** | 0.015 (0.008 to 0.023) | <0.001 |
| **Baseline Dialysate IL-6 (log transformed pg/ml)** | 0.048 (0.028 to 0.068) | <0.001 |
| **Urine Volume (L)** | 0.011 (0.000 to 0.021) | 0.04 |
| **Peritonitis with Biocompatible Solutions** | -0.014 (-0.033 to 0.005) | 0.11 |
| **Peritonitis with Standard Solutions** | 0.020 (0.013 to 0.027) | <0.001 |

Multilevel multivariable model demonstrating the effect of covariates on PSTR. Coefficients demonstrate the adjusted rise in PSTR for a 1 unit change in covariate. For 1 litre of urine volume there is an increase of 0.011. For an increase of 2 years time, the change represents the sum of the two coefficients for the solution type e.g. standard solutions have a change of 0.0009\*2\*2-0.028\*2. At the start of PD, biocompatible solution use was associated with slower PSTR, increasing significantly over the next 2-3 years then flattening off, whereas for standard solutions a trivial reduction in PSTR then a slight rise was seen in the model (negative linear and positive quadratic time coefficients). Independent of these trends, use of icodextrin, baseline inflammation and peritonitis were all associated with faster PSTR, the latter only when exposed to standard solutions. Higher Dialysate Dextrose concentration was associated with faster PSTR after a prolonged period on PD (positive interaction with time) but little association at the start. Covariates not included in the final model as not significant include APD/CAPD use, plasma IL-6, gender, age and comorbidity status. Centre had a significant effect (range of coefficient -0.13 to 0.001). \* p values for overall effect from Wald statistic.

**Figures and Legends**

*Figure 1. Flow diagram showing inclusion of participants in analysis*

n –number of patients, m – number of measurements

*Figure 2. Change in solute transport for standard (A) and biocompatible (B) solutions with comparison of average change (C) for both solutions*

Solid grey and black lines represent the adjusted PSTR for standard and biocompatible solutions respectively with dotted lines for 95% CI. Standard solutions remain stable then demonstrated a slight rise. Biocompatible solutions have a slower PSTR at baseline but a steeper increase in PSTR over time, this stabilises at 2 years. PSTR values are adjusted for centre, Icodextrin use, daily dextrose concentration, baseline dialysate IL-6, peritonitis and urine volume. There were 43 (60%) and 219 (60%) patients in the biocompatible and bioincompatible groups respectively at 2 years follow up and 11 (15%) and 96 (33%) at 4 years. Modelling of biocompatible solutions was stopped at 4 years due to the low patient numbers beyond this.

*Figure 3. Changes in solute transport for standard solutions by dialysate dextrose concentration*

Trajectory over time for low (1.33%, 25th centile), medium (1.5%, 50th centile) and high (1.93 %, 75th centile) daily dextrose concentration. High dextrose concentration is associated with an increase in PSTR over time compared to low or medium concentrations. This effect of dialysate dextrose concentration on the trajectory of PSTR has strong evidence (p<0.001) in the model.

*Figure 4.* *Change in PSTR over time and impact of time varying covariates*

Unadjusted PSTR (D/P Cr) and 95% Confidence Intervals over time by solution type A – Standard Solutions, and B – Biocompatible Solutions. C Effect of constant average vs. time varying actual values on sample patient selected using random number generator.

*Figure 5. Changing variance of PSTR with time on peritoneal dialysis*

1, unadjusted model. 2, Model adjusted for PD IL6. 3, Model adjusted for biocompatibility and PD IL6. 4, Fully adjusted model. The unadjusted model shows a reduction in variability over time, which is reduced further in the adjusted models. This demonstrates most of the reduction in variance over time can be accounted for by covariates within the analysis.