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Changing prescribing practice in CAPD patients in Korea: increased utilization of low GDP solutions improves patient outcome

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Abstract

Background. Novel, biocompatible peritoneal dialysis (PD) solutions have become available in recent years. In 2001, low glucose degradation products (GDP), neutral pH solutions became commercially available in Korea. To date, there are no reports regarding the large scale adoption of these solutions in clinical practice and regarding what, if any, impact these solutions have on patient outcomes.

Methods. Using a database of almost 4000 patients treated by PD in Korea, we conducted a prospective, longitudinal observational study documenting the patterns of use of one novel low GDP solution (balance®, Fresenius Medical Care, St Wendel, Germany) in 1909 PD incident patients between 1 January 2002 and midyear 2005. Outcomes including patient and technique survival and peritonitis rates were analysed using univariate and multivariate analysis.

Results. Prescription of low GDP solutions reached between 70 and 80% by the year 2003 and persisted at this level. Patients prescribed low GDP PD solution tended to be younger and were more likely to be treated in centres with larger enrolment in the database. Survival of diabetic patients treated with the new PD solution was identical to that of the non-diabetic patients treated with standard PD fluids (PDF) and treatment with low GDP PDF independently reduced the relative risk (RR) of death (RR = 0.613; CI 0.50–0.74; $P < 0.00001$) in a proportional hazards model which included age, diabetes and centre experience. In a univariate analysis, low GDP PD solution was associated with a longer technique survival ($P = 0.049$) but this effect was not significant in multivariate analysis. No significant differences in peritonitis-free interval or peritonitis rate could be attributed to the prescribed PDF.

Conclusion. Prescription of low GDP, pH-neutral PD solutions has rapidly increased in Korea. This change has resulted in a significant improvement in patient and technique survival without any measurable change in peritonitis incidence or rate. Reasons for the improved patient survival cannot be determined from this analysis and require further study.

Keywords: CAPD; glucose degradation products; patient survival; pH neutral; prescribing practices

Introduction

In recent years, novel peritoneal dialysis fluids (PDFs) with neutral pH and low concentrations of glucose degradation products (GDP) have become commercially available [1]. GDPs have been established as major factors in peritoneal fluid bioincompatibility [2,3] and a large body of experimental evidence from *in vitro* and *in vivo* studies [1–6] and recent clinical results [7,8] suggest that these novel PDFs provide promise of improved outcomes for PD patients. In Korea, low GDP solutions were registered for reimbursement in July 2001.

In cooperation with the supplier of one such PD solution [balance® provided by (FMCK) Fresenius Medical Care, Korea], a web-enabled database was established about this time to monitor PDF prescription and patient events including patient and technique survival and peritonitis rates. The results of our preliminary experience with the novel PDF were published previously [9]. With more than one year's additional experience and a considerably larger

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dataset, we describe here a trend towards preferential prescription of low GDP PDF and confirm that the change in the prescription practice is associated with the superior patient survival.

Patients and methods

The database used for this analysis was described previously [9]. Briefly, this is a web-enabled database in which all patients prescribed any continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) FMCK are recorded. Patient data were entered by the PD centre staff assisted as required by the clinical coordinators employed by FMCK. Recorded data include unique patient and hospital identifiers, patient age, sex and cause of end-stage renal disease (ESRD), modality [CAPD, continuous cycling peritoneal dialysis (CCPD), nocturnal intermittent peritoneal dialysis (NIPD)], dates for initiation of PD, change of prescription, ceasing PD and all peritonitis episodes. Additionally, data are captured for the reasons for stopping PD and for causes of death and modality change. Where a patient is converted to a product other than those provided by FMCK, the product type is recorded but further events for those patients are not recorded. Also, further events were not recorded for patients converted to haemodialysis and for those who received a renal transplant.

On 1 November 2005, the database included 3722 individual patient records. From this, we identified 2317 incident patients between 1 January 2002 and 30 May 2005. We excluded 43 patients treated by automated PD and 60 juvenile patients (age <18 years) leaving an analysis data set of 2214 incident CAPD patients. Of these, within the period of study, 305 patients underwent a change of prescription—from standard to low GDP PDF. Since the database did not record reason for prescription preference or change, these 305 patients were excluded from the final analysis. As shown in Table 1, the excluded patients were younger, were more likely to be from more experienced centres (see subsequently) and had significantly better 1, 2 and 3-year survivals (Kaplan–Meier method) than the 1909 patients included for analysis.

The study close date was set as 30 September 2005. The patients were treated in 104 PD centres. Of these, 13 centres that contributed more than 40 patients to the data set (range 41–193) and accounted for 55% of the total population were classified as 'more experienced' and the remaining centres as 'less experienced'.

Statistical analysis

As appropriate, data summaries are provided as means (and standard deviation), medians (and ranges) or proportions (percentages). Comparisons of treatment groups were undertaken with standard parametric and non-parametric tests as appropriate to the data type. Univariate analysis of survival times was by the Kaplan–Meier life-table method and significance of differences tested by log rank test. Multivariate analysis of survival times was undertaken by Cox proportional hazards modelling with forward stepwise entry of variables and variable inclusion in the model determined by the value of the likely ratio statistic. For each model, proportionality of hazards was tested by visual observation of the log-minus-log (LML) plots. All analyses were performed using SPSS version 14.0 (SPSS, Chicago, IL, USA).

Table 1. Selected characteristics of patients included in and excluded from the final data set for analysis

		Included	Excluded	*P*-value
Number		1909	305	
Prescription	Standard	514	–	
	Low GDP	1395	–	
	Change	–	305	
Male/Female		1054/855	161/144	0.429
Diabetic		993	149	0.305
Centre experience	Less	710	79	<0.0001
	More	1199	226	
Mean age (SD)		56.94 (13.73)	54.34 (13.23)	0.002
Survival	1 year	82%	96%	<0.0001
	2 year	71%	89%	
	3 year	62%	87%	

Centre experience categorized according to number of cases included in the data set: more experience >40 cases.

Results

Changing prescription patterns

The new PD solution, balance®, was introduced in Korea mid-year 2001. As shown in Figure 1, the percentage of initial prescriptions of the low GDP PDF exceeded 45% of new patients by quarter 1(Q1), 2002. Within two years, 81% of new patients were prescribed low GDP PDF in the Q1 of year 2004 and the prescription preference remained in the range 70–80% thereafter.

Patient characteristics

As shown in Table 2, 1395 patients were prescribed low GDP PDF and 514 standard PDF. Patients prescribed low GDP PDF were younger (56.32 ± 13.42 years) than patients on standard solution (58.67 ± 14.4; $P = 0.001$) and included a higher proportion of patients from more experienced centres (65 *vs* 56%; $P < 0.0001$). Distributions by gender and diabetes mellitus as the recorded cause of ESRD were similar in both groups.

Patient outcomes

By the end of the study period, 1119 patients were alive and being treated with a product provided by FMCK. The status of all patients on 30 September 2005 according to the prescribed PDF is shown in Table 3. It is evident that 55% of the deaths were attributed to cardiac and vascular disease and 8.4% to sepsis or infection. The proportion of cardiovascular deaths was higher in patients who prescribed low GDP PDF (61.5 *vs* 46.5%) but the difference was not statistically significant ($P = 0.387$). Similar proportions

Fig. 1. Changing proportion of patients prescribed standard and low GDP peritoneal dialysis fluids (PDF) over the period of the study—January 2002–May 2005.

Table 2. Selected characteristics of patients according to the prescribed PD solution

		Prescribed PD Solution		
		Standard	Low GDP	*P*-value
Number		514	1395	
Male/female		301/213	753/642	0.074
Diabetic		273	720	0.298
Centre experience	Less	224	486	< 0.0001
	More	290	909	
Mean age (SD)		58.67 (14.40)	56.32 (13.42)	0.001

Centre experience categorized according to number of cases included in the data set: more experience >40 cases.

Table 3. Status of all patients on 1 October 2005 (at the end of the study)

	Prescribed PDF			
	Standard		Low GDP	
	n	%	*n*	%
Alive	223	43.4	896	64.2
Dead	176	34.2	265	19.0
To haemodialysis	54	10.5	117	8.4
To renal transplant	30	5.8	59	4.2
To other product	19	3.7	38	2.7
Recovered renal function	10	1.9	13	0.9
Other/unknown	2	0.4	7	0.5

from each group received a renal transplant or were transferred to haemodialysis. Of the 171 patients converted to haemodialysis (54 from standard PDF and 117 from low GDP PDF), 49 (29%) transfers were attributed to peritonitis and 26 (15%) to ultrafiltration failure; no differences in these proportions were identified for the prescribed PDF. Of the 57 patients whose prescription was changed to a product not provided by FMCK, 31 (54%) were prescribed icodextrin. The proportions of patients prescribed icodextrin were similar for both groups (standard 1.2% and low GDP 1.8%; $\chi^2 = 0.918$; $P = 0.338$).

Mortality and technique failure rates

The unadjusted mortality rate (expressed per 100 patient years) for patients treated with low GDP PDF was significantly lower than that of the patients treated with standard PDF (14.5 *vs* 29.3; $P < 0.0001$), whereas no difference was detected for unadjusted technique failure rates (low GDP 6.8/100 years; standard 9.4/100 years; $P = 0.184$).

Patient and PD technique survivals

In univariate analysis (Kaplan–Meier), older age and diabetes were associated with worse patient survival, whereas treatment in a more experienced centre and treatment with low GDP PDF were associated with improved survival (data not shown). When patients were stratified according to diabetic status, the use of low GDP PDF was associated with superior survival for diabetic and non-diabetic patients (all *P*-values <0.0001). Moreover, the survival plot for diabetic patients treated with low GDP PDF was identical to that for non-diabetic patients treated with standard PDF ($P = 0.913$: Figure 2).

In a multivariable Cox proportional hazards model which included patient sex, age, diabetic status, centre experience, history of peritonitis (any *vs* none), prescribed PDF and the interaction between prescribed PDF and centre experience, there was an independent and significant reduction in hazard of death (relative risk) associated with the use of low GDP PDF. As expected, older age and diabetes were associated with increased relative risk of death and

death risk was significantly reduced for patients treated in more experienced PD centres. There was no significant interaction for PDF and centre experience (Table 4 and Figure 3).

PD technique survival was analysed in a similar manner to patient survival. The measured event was treated in two ways. In the first method, the event was the time to conversion to haemodialysis with deaths and renal transplants censored. In the second method, the event was defined as death or conversion to haemodialysis and renal transplants were censored. For the first method of analysis in univariate analysis by Kaplan–Meier prescription low GDP PDF was associated with a longer technique survival (at 3 years 84 *vs* 77% for standard PDF; $P = 0.049$), but this difference was not retained in a Cox multivariable model (same variables as aforementioned) where only centre experience (more *vs* less) was found to be independently predictive of better technique survival.

In the second method of analysis, effectively an analysis of 'PD success', in both univariate (Kaplan–Meier) and multivariable (Cox proportional hazards) analyses, significantly longer PD technique survival was identified for patients treated with the low GDP solution. The results are shown in Table 5 and Figure 4 where the survival plots represent the survivals at the mean of all variables included in the model. As shown in Figure 4, the prescription of low GDP solution prolonged the technique survival by more than 1 year compared with the prescription of standard solution. In an additional model where the conversion of the patients' prescription to icodextrin (as indicating a failure of standard PD therapy) was included as a technique failure, the results of univariate and multivariable technique survival analysis were essentially unchanged (data not shown).

Peritonitis rates and peritonitis-free survival

Of the 1909 patients, 460 (24%) suffered at least one peritonitis event. The peritonitis rates were 0.29 per year (1 per 41 months) for standard PDF and 0.26 per year (1 per 46 months) for low GDP PDF ($P = 0.479$). There was no difference in peritonitis-free interval (Kaplan–Meier method) for the two PD solutions.

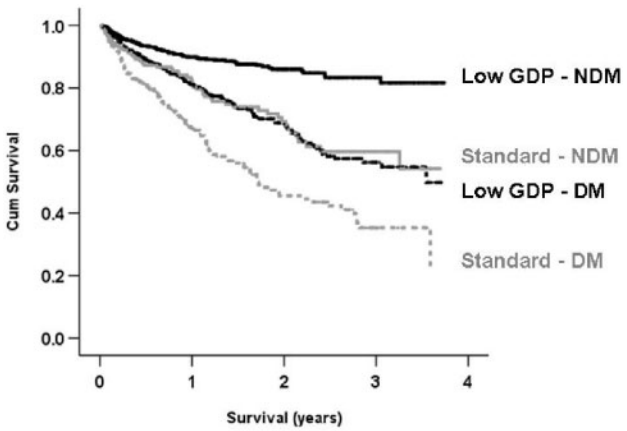

Fig. 2. Plots of probability of patient survival by univariate analysis (Kaplan–Meier method) by diabetic status and prescribed PD solution (standard PDF and low GDP PDF).

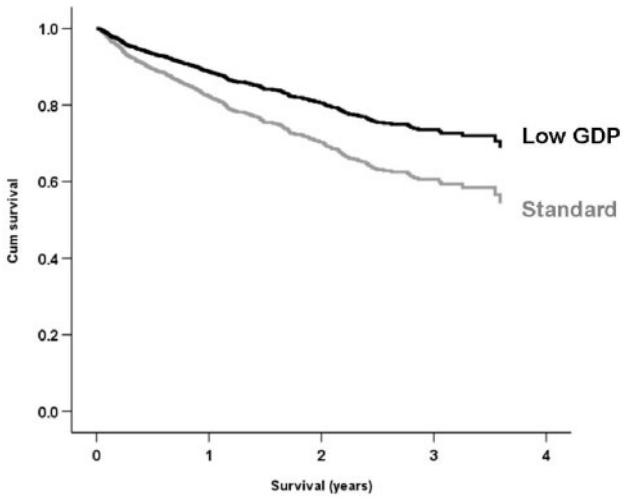

Fig. 3. Plots of patient survival at the mean of all included variables (covariates) in the Cox proportional hazards model comparing patients treated with standard and low GDP PD solutions. Details provided in Table 4.

Table 4. Multivariable Cox proportional hazards model for time to death

	Confidence interval			
	RR	Lower	Upper	*P*-value
PD solution (Low GDP *vs* standard)	0.613	0.504	0.744	0.00000
Age (per year older)	1.062	1.052	1.071	0.00000
Diabetes (yes *vs* no)	1.690	1.378	2.072	0.00008
Centre experience (more *vs* less)	0.678	0.559	0.823	0.00000

Variables entered: age, diabetes, centre experience, peritonitis (any *vs* none), year enrolment, PD solution, interaction between PD solution and centre experience: RR, relative risk of death. Centre experience categorized according to number of cases included in the dataset: more experience >40 cases.

Discussion

We describe here a rapid change in PDF prescription practice in over 1900 incident CAPD patients in Korea treated during the period 2002 through midyear 2005. Patients prescribed low GDP PDF were younger than those prescribed standard PDF (Tables 1 and 2) and centres with more patients enrolled in the database appeared more likely to prescribe the low GDP PDF. Thus, patient age and a 'centre effect' probably contribute to the results we describe, but the benefit of low GDP prescription on patient survival retained independence and significance in a multivariable survival analysis that included both variables.

In this population, 76% of the patients never experienced peritonitis which is the same proportion reported as peritonitis-free by Kim *et al*. [10] from the Korean Renal Registry. The peritonitis rate of our patients was low (<0.3 episodes per year) but we could not identify any effect of low GDP PDF in reducing peritonitis rate or prolongation of the peritonitis-free interval.

We cannot categorically state that there was no negative selection of the patients prescribed and maintained on standard PDF. Kim *et al*. [10], reporting for the Korean ESRD registry, described a combined patient and technique survival rate for Korean CAPD patients of 31.9% at 3 years. It is likely that almost all of those patients were treated with standard PDF. In a combined technique and patient survival, using Kaplan–Meier analysis and where technique failure was defined as conversion to haemodialysis, we found a 3 year survival of 34% of the patients treated with standard PDF (data not shown), similar to the total survival reported by Kim *et al*. [10]. This finding argues against significant negative selection of our patients treated with standard PDF.

On the other hand, was there a positive selection of a lower risk group for prescription of the low GDP PDF? These patients were younger by 2.4 years on an average, but included a similar proportion of diabetic patients. Based on an upper bound for the effect of age on survival (7.1% increased risk of death for each additional year age), younger age might have accounted for ~18% (less than half) of the 39% reduced risk of death associated with the prescription of low GDP PD solution.

Those centres with more patients included in this data set and thereby defined as more experienced were more likely to prescribe the low GDP PDF, and both by univariate and multivariable analysis, experienced superior technique and patient survival than less-experienced centres. However, in multivariable analysis, the effect of the PDF on patient and technique survival remained robust and independent of the centre effect.

Two approaches are used to define technique failure (or success) in PD. In one, modality conversion to haemodialysis is the measured event and deaths are censored, whereas in the other, deaths and conversions to haemodilaysis are the events. Using the latter method, our analysis indicates significantly superior technique survival for low GDP solution in univariate and multivariable analysis, whereas using the former method, a significantly improved technique survival for low GDP solution detected in Kaplan–Meier analysis failed to retain significance in multivariable analysis where centre experience was the solitary factor of significance.

A significant contributing cause to PD technique failure is membrane failure for ultrafiltration—ultrafiltration failure (UFF). One therapeutic alternative for treating UFF is recourse to prescription of icodextrin. Thus, the requirement for prescription of icodextrin might be considered a 'failure' of standard PD. We detected no difference in the rates of prescription of icodextrin (low GDP PDF 1.8% and standard PDF 1.2%), and in an analysis that extended the definition of technique failure to include patient

Table 5. Multivariable Cox proportional hazards model for time to technique failure (method 2: see text)

	Confidence interval			
	RR	Lower	Upper	*P*-value
PD solution (Low GDP *vs* standard)	0.638	0.540	0.753	0.00000
Age (per year older)	1.040	1.033	1.047	0.00000
Diabetes (yes *vs* no)	1.461	1.234	1.730	0.00001
Centre experience (more *vs* less)	0.625	0.531	0.736	0.00000

Variables entered: age, diabetes, centre experience, peritonitis (any *vs* none), year enrolment, PD solution, interaction between PD solution and centre experience: RR, relative risk of death. Centre experience categorized according to number of cases included in the data set: more experience >40 cases.

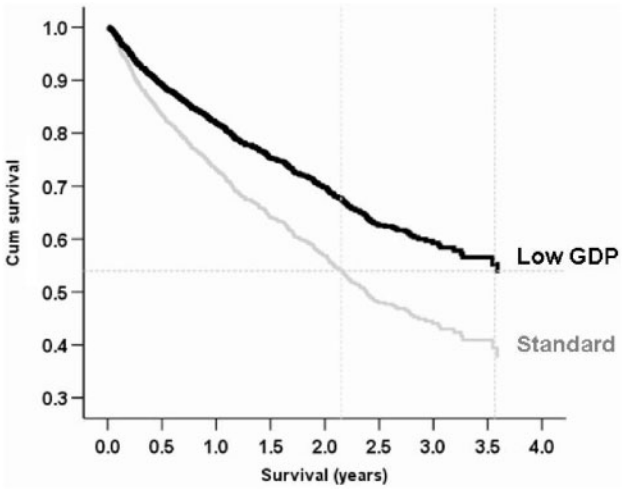

Fig. 4. Plots of PD technique survival (cases censored at conversion to haemodialysis) at the mean of all included variables (covariates) in the Cox proportional hazards model comparing patients treated with standard and low GDP PD solutions. Details provided in Table 5. Patients treated with low GDP PDF have a technique survival ~ 1.4 years greater than those prescribed standard PDF.

prescription of icodextrin, the technique survival analysis by univariate and multivariable analysis was not significantly changed (data not shown).

Because of the limitations imposed by the design of the database, we cannot identify a mechanism for the improved survival imparted by the prescription of the low GDP solution.

Recent reports from mainly observational data have identified various associations for higher mortality in PD patients including impaired nutrition, systemic inflammation and, probably most dominantly, loss of residual renal function [11–13]. In the Euro-Balance Trial, Williams *et al*. [8] noted better preservation of residual renal function in a cross-over study of balance® and standard PDF and reported preliminary results of the DIUREST study. Haag-Weber *et al*. [14] described better preservation of residual renal function for patients treated with another low GDP solution (Gambro Trio®) compared with patients on standard PDF [14]. We are aware of an ongoing randomized controlled trial that is specifically examining the possible effect of low GDP PDF on the rate of change in residual renal function [15]. Hopefully, this study (results expected in 2008) will clarify this critically important question.

Of particular interest was the effect of low GDP PDF on the survival of diabetic patients who accounted for 51% of this cohort. In effect, the probability of survival of diabetic patients treated with low GDP PDF was the same as that of non-diabetic patients treated with the standard PDF (Figure 2). A possible and testable hypothesis for the survival advantage associated with low GDP PD solution prescription might relate to advanced glycation. In the Euro-Balance Trial, Williams *et al*. [8] reported significant lowering of serum levels of the advanced glycation end-products (AGE), carboxymethyllysine and imidazolone, in patients treated for 3 months with the low GDP solution, balance®, when compared with the AGE levels on standard PDF. Greater and more sustained reduction in circulating AGE levels might be expected in our patients who were treated for up to 3½ years with low GDP PDF. Advanced glycation has been implicated in the causation of microvascular and macrovascular disease in diabetics and in age-related kidney disease. Furthermore, absorption of GDPs from the peritoneum may promote systemic advanced glycation [16,17]. AGE–AGE receptor (RAGE) binding induces transcription for increased production of inflammatory cytokines, adhesion molecules, growth and pro-fibrotic factors from monocytes, endothelial cells and mesothelial cells [18]. AGE have been implicated in chronic allograft nephropathy, a model of progressive loss of renal function [19] and reduction of circulating AGE by dietary manipulation protects the kidney function in the aging rat [20]. Thus, it is plausible that reduction in systemic AGE levels exerts a protective effect on native renal function, thereby improving patient survival. This hypothesis should be tested in an appropriately designed clinical study.

Conclusion

We report a major increase in the prescription of low GDP PDF in a large cohort of incident CAPD patients in Korea following their commercial introduction in our country. As yet, we have not been able to identify factors determining prescription choice. This change in PD prescription practice has resulted in a significant improvement in patient outcomes.

These results need to be confirmed in other nations by appropriately designed studies.

Given that prescribing nephrologists might be reluctant to undertake wholesale prescription of these new solutions on the evidence now available, our data suggest that the diabetic CAPD candidate might be a preferred target for an early adoption.

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Conflict of interest statement. None declared.

(See related article by Bargman. *Nephrol Dial Transplant* 2006; 21: 2684–2686.)

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