Analysis of factors associated with variability in haemodialysis adequacy

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Abstract

**Background.** Delivered dialysis dose measured as Kt/V is widely accepted as an important factor affecting mortality on haemodialysis. It is currently measured relatively infrequently in most units for pragmatic reasons. We have previously shown that significant variation occurs within individuals which often makes the difference between dialysis that would be considered adequate, and inadequate. The aim of this study is to delineate which factors are responsible for the observed variation.

**Methods.** We studied 1109 treatments in 109 patients, mean age 59.9 years, mean dry weight 71.8 kg. Depurated volume (Kt) was measured by ionic dialysance for each treatment. Kt and other relevant treatment-related variables were automatically recorded on a central server. Multivariate analysis using mixed models with backwards elimination was used to analyse the determinants of Kt. Kt/V was not used, in order to avoid introducing error in the determination of V.

**Results.** The analysis indicated that the following were independent determinants of Kt: blood pump speed, time, minimum and mean arterial line pressure, both maximum and minimum venous line pressures and total ionic mass balance.

**Conclusion.** This analysis suggests that the variation in adequacy that occurs within an individual is multifactorial. It confirms the importance of effective vascular access, prescription of and adherence to adequate time on dialysis, and reinforces the impact of degree of sodium removal. In clinical practice absolute control of these variables is not possible in every dialysis session and some degree of variability in Kt is therefore inevitable. Monitoring of adequacy thus requires more frequent assessment of Kt than is currently performed. Online monitoring of ionic dialysance achieves this.

**Keywords:** haemodialysis adequacy; ionic dialysance; modelling; multivariate analysis; online clearance

Introduction

It is now well recognized that an adequate delivery of haemodialysis (HD) dose (as measured by Kt/V derived from urea reduction) is a crucial determinant of clinical outcome for chronic HD patients [1–3]. This requires both prescription of an adequate dose of HD and regular assessment that the delivered treatments are adequate [4,5].

Monitoring of Kt/V by urea reduction requires blood sampling before and after HD. The logistical problems involved with this, and the inconvenience of measures taken to reduce the effect of post-dialytic rebound in serum urea, ensure that this is an infrequently taken measure in the majority of chronic HD units. NKF-DOQI guidelines recommend a monthly interval. They acknowledge that this is a pragmatic rather than an ideal recommendation [6], and that there is often a delay between measurement and reporting of Kt/V of up to a week. Increased frequency of measurement of Kt/V is only suggested in cases of underdialysis.

Measurement of adequacy is now achievable for every dialysis session, with results available immediately through the use of online conductivity monitoring and measurement of ionic dialysance [7–9]. We have previously reported marked intra-patient variation in dialysis adequacy using this technique [10], confirming previous reports of similar variation using conventional serum based measurements of adequacy [4,5]. In our previous study of 316 treatments in 26 patients, a mean Kt/V of 1.0 was measured by ionic dialysance with a mean intra-individual variation of 13%. Fifty-five percent of the patients we studied had variation within the 1 month study period that, depending on when a single measurement of adequacy by ionic dialysance had been measured, would have altered their status as adequately or inadequately dialysed. Further study has also
suggested that this variability leads to a systematic overestimate of dialysis adequacy due to alterations in the behaviour of patient and nursing staff on the day of adequacy measurement [11]. This implies that infrequent sampling will often give an inaccurate reflection of achieved adequacy, and that this will frequently overestimate the overall level of urea reduction.

This study aimed to extend the previous study by using online monitoring to examine the variation in delivered adequacy, and then to establish those factors that may contribute to this variation and the importance of their influence on the observed variation in delivered dialysis dose.

Subjects and methods

Patients

109 chronic HD patients were studied [mean age 58.3 years (range 22–85 years), dry weight mean 73.8 kg (range 38–192 years), 78 male, 31 female] over 1109 treatments. Appropriate ethical approval for the study and consent from the patients was obtained. All patients were studied within the main HD unit at Derby City General Hospital. Patients were advised to restrict their dietary sodium intake to 80–100 mmol/day and given advice on fluid restriction appropriate to their individual requirements.

Haemodialysis schedule

HD was performed using Hospal Integra® dialysis monitors. All patients were dialysed for 4 h treatment sessions, three times per week. Ultra pure dialysate was generated using water having undergone dual pass treatment. Patients were dialysed using bicarbonate buffering, a dialysate sodium concentration of 140 mmol/l and a dialysate flow rate of 500 ml/min. HD used either low-flux haemophan polycarbonate membranes (Hospal HG 500–700) or mid-flux cellulose diacetate membranes (Hospal Diacepal 20), no dialysers were reused, and a linear ultrafiltration profile was used throughout.

Monitoring

All treatments were prescribed on a central server and downloaded to the monitor for each dialysis session. All monitors were equipped with Diascan® conductivity monitoring modules. The Diascan module changes inlet conductivity every 30 min and records the change in conductivity at a second conductance meter at the dialysate waste. From this change, ionic dialysance and plasma conductivity can be calculated automatically. Because conductivity is related to ion concentration it is possible to substitute one for the other in further calculations. As the transfer characteristics of sodium and urea are similar, the ionic dialysance reflects the clearance of urea (corrected for recirculation). This can then be expressed as Kt/V using a value for V entered into the model by the clinician. Ionic dialysance derived Kt/V has been validated as an effective and accurate system for the assessment of dialysis adequacy (as measured by Kt/V) [8,9]. Ionic mass balance (IMB), indicating total sodium flux in mmol, is also derived from these measurements, with positive values indicating removal of sodium from the patient. All treatments were monitored for changes in relative blood volume, by the use of continuous measurement of haemoglobin concentration (Hemoscan®). Data pertaining to the dialysis session were uploaded to patient-specific files at the end of each treatment for subsequent analysis. Data are from those dialysis sessions recorded over a 6 month period.

Statistical analysis

Data were analysed using SPSS version 11. The mixed models were fitted using R 1.7.1 [12] with version 3.1.43 of the nlme package [13]. Backwards elimination was used with a cut-off of P = 0.05. The variables listed in Table 1 were used to predict Kt with patient as a random effect. Data are expressed as mean ± SEM unless otherwise stated.

Results

A mean of 10 (1–43) ± 0.99 measurements of Kt for each of 109 patients yielded a mean Kt for all treatments of 42.61 (42.1–43.1) ± 8.1 (95% confidence intervals, SD) (Figure 1). Prescribed Kt for those sessions using HG700 dialysers was 62.2 l, and no patient achieved this. Descriptive statistics for the independent variables used in the analysis are shown in Table 1. All were normally distributed.

Kt was used as the response variable and the variables in Table 1 were used as possible predictors. The following were left in the final equation: blood pump speed (Qb), time (of dialysis session), minimum and mean arterial line pressures, both maximum and minimum venous line pressures and total IMB. The variables were eliminated by hand on the basis of their significance levels in the order: maximum RBV reduction, mean venous pressure, change in plasma conductivity, pre-dialysis plasma conductivity, heparin dose, maximum arterial pressure and total weight loss.

Table 1. Descriptive statistics for those variables used to predict Kt, with patient as a random effect

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kt (l)</td>
<td>42.8</td>
<td>8.1</td>
</tr>
<tr>
<td>Blood pump speed (ml/min)</td>
<td>308</td>
<td>61.8</td>
</tr>
<tr>
<td>Time (min)</td>
<td>236</td>
<td>10.4</td>
</tr>
<tr>
<td>Total heparin dose (units)</td>
<td>3932</td>
<td>1622</td>
</tr>
<tr>
<td>Pre-dialysis plasma conductivity (mS/cm)</td>
<td>14.12</td>
<td>0.28</td>
</tr>
<tr>
<td>Post-dialysis plasma conductivity (mS/cm)</td>
<td>13.72</td>
<td>0.15</td>
</tr>
<tr>
<td>Change in plasma conductivity (mS/cm)</td>
<td>0.40</td>
<td>0.19</td>
</tr>
<tr>
<td>Maximum relative blood volume reduction (%)</td>
<td>-5.4</td>
<td>3.30</td>
</tr>
<tr>
<td>Mean arterial line pressure (mmHg)</td>
<td>-124</td>
<td>39</td>
</tr>
<tr>
<td>Maximum arterial line pressure (mmHg)</td>
<td>-105</td>
<td>40</td>
</tr>
<tr>
<td>Minimum arterial line pressure (mmHg)</td>
<td>-141</td>
<td>47</td>
</tr>
<tr>
<td>Mean venous line pressure (mmHg)</td>
<td>133</td>
<td>31</td>
</tr>
<tr>
<td>Maximum venous line pressure (mmHg)</td>
<td>148</td>
<td>35</td>
</tr>
<tr>
<td>Minimum venous line pressure (mmHg)</td>
<td>123</td>
<td>31</td>
</tr>
<tr>
<td>Total weight loss (kg)</td>
<td>1.93</td>
<td>0.80</td>
</tr>
<tr>
<td>IMB (mmol)</td>
<td>349</td>
<td>145</td>
</tr>
<tr>
<td>Diffusive IMB (mmol)</td>
<td>79</td>
<td>81</td>
</tr>
</tbody>
</table>
The final model is shown in Table 2. As can be seen, the effects for all of these variables have 95% confidence intervals which do not include zero.

Time since study entry was also added but was not an important source of variation either as a fixed or random effect. Each of the variables listed in Table 1 was also entered as a random effect but these changes did not lead to important changes in the coefficients and for simplicity we have not included them in the final model. In the random effects the variation due to patients is similar to that within patients (2.99 vs 3.49) suggesting that the mixed model approach was necessary. Kt results were also analysed for the effect of gender. Female patients had a predicted value of Kt which was 2.45 less than male patients (95% confidence interval from 4.04 to 0.86 less). The only variable which interacted with gender was time of dialysis session.

The individual results for Qb are displayed (Figure 2), as well as those for IMB (Figure 3), demonstrating the broad range of these variables both between and within patients. Time of dialysis session is also displayed (Figure 4), demonstrating a high degree of adherence to the prescription (mean time of dialysis session 236 ± 11 min).

Discussion

This study confirms previous findings of considerable variability in delivered Kt. The results indicate that the degree of intra-patient variability in the efficiency of blood purification is influenced most strongly by time on dialysis, but also by a combination of measures related to vascular access function (blood pump speed,
Fig. 2. Variability in blood pump speed over the study period, showing median, quartiles, maximum and minimum for individual patients arranged in ascending order by median blood pump speed.

Fig. 3. Variability in IMB over the study period, showing median, quartiles, maximum and minimum for individual patients, arranged in ascending order by median IMB.
minimum and mean arterial line pressures, and both maximum and minimum venous line pressures). The other major influence on the model was the degree of sodium removal measured as total IMB.

This study analysed the variability in Kt rather than Kt/V to remove the error inevitably introduced by including an estimate of V in the calculation. There is no accepted method for measuring V in routine use in haemodialysis, and use of ionic dialysance to measure Kt, requires a value for V to be calculated by the clinician. Most methods used for estimating V, including those based on the formulae described by Watson et al. [14], take no account of the variable state of hydration in a patient undergoing haemodialysis. The value chosen for V must be an estimate, hence introducing a degree of unnecessary inaccuracy and potential further variability into the equation. Using Kt alone also focuses the analysis on intra-patient rather than inter-patient variation by reducing the influence of patient-specific factors such as age, weight and sex. Dialyser clearance remained constant for virtually the entire cohort during the study, and dialyser clearance was therefore treated as a patient-specific factor, and was not entered into the model. The variable efficiency of blood purification is therefore the focus of this study. Measurement of Kt/V with this method has been shown to correlate closely with urea-based measurements [8,9].

Our study emphasizes the role that lack of adherence to time prescribed plays in determining the variation of dialysis adequacy. Other studies have shown this effect, as well as indicating that there is a tendency to stick more rigorously to the prescription on the days of formal adequacy measurement [11,15,16], thus suggesting that any variability will tend to lead to an over-estimate of adequacy. Despite the relative lack of variation between patients (Figure 4), time still had a profound effect on Kt, indicating the importance of ensuring that patients remain on dialysis for the full time prescribed. All patients in this study were prescribed 240 min of dialysis, which remained unchanged during the study, and there was a high degree of adherence to the prescription.

A range of measures related to vascular access were also important in predicting Kt, an effect that was seen consistently in all analyses. Qb, mean and maximum arterial line pressures and minimum venous line pressure have a positive correlation with Kt while maximum venous line pressure correlates negatively as would be expected. These factors emphasize the known importance of vascular access quality in determining dialysis adequacy [15,16]. Qb, however, is not simply determined by the quality of the vascular access, but also by the pump speeds that both the patient and dialysis nurse are willing to tolerate. A higher pump speed may be associated with an increased risk of alarms, for example, arterial/venous line pressure alarm, and there is a tendency to reduce the pump speed to avoid this. There is also a patient perception that an increased pump speed leads to instability and
Symptoms, resulting in patient pressure to reduce pump speed. Nurse attention to Qb is potentially a potent factor explaining the observed improvement of Kt/V on days when dialysis adequacy is measured [11]. We did not analyse the effect of vascular access type, which has been shown previously to affect adequacy [17]. Rather, the analysis demonstrates that the overall function of vascular access is the single most important determinant of variability in delivered dialysis dose.

Sodium removal, as measured by total IMB, appears to influence Kt. This is not simply due to the contribution that convective clearance of urea makes to overall adequacy. Ultrafiltration volume, which correlates directly with convective loss, was not a predictor of Kt. IMB therefore represents the influence of the combination of diffusive and convective sodium loss. Sodium movement across the dialysis membrane is related to urea movement [7] and the relationship seen between Kt and IMB in this study may reflect membrane factors, such as clotting, which would affect movement of both sodium and urea. IMB and Kt are both derived from ionic dialysance measurements, and it is possible that the correlation seen may represent a degree of mathematical artefact. Plasma conductivity, derived from the same measurements, did not, however, enter the model, suggesting that this is unlikely. Sodium removal has not previously been described as having an influence on dialysis adequacy, largely due to a previous lack of a robust and simple methodology with which to study it. This novel finding is worthy of further investigation.

The effect of gender on Kt is separate from gender-related differences in V, and seems to relate to reduced time of dialysis session for female patients despite identical prescribed time on dialysis. The monitoring system was not configured to routinely record blood pressure, and this was therefore not included in the analysis. Blood pressure may well also correlate with Kt, consistent with the hypothesis of tissue underperfusion, in which haemodynamic instability leads to underperfusion of tissue compartments, which are then relatively inaccessible during HD [18,19].

This model does not reflect clearances of molecules not measured by ionic dialysis Kt such as phosphate and β-2 microglobulin. Kt measured by conductivity monitoring reflects movement of ions and small molecules, and these results cannot therefore be extrapolated to middle or large molecule clearances.

The further analysis of the determinants of the demonstrated variability indicates which factors should be focussed on in attempting to ensure consistent delivery of adequate dialysis. These include factors already widely accepted to influence adequacy such as dialysate permeability and surface area, blood and dialysate flow, as well as actual time on dialysis for patients who have inadequate dialysis, as seen in both previous studies [15,16] and in the most recent DOQI guidelines [6]. This study reinforces the importance primarily of adherence to time prescribed on dialysis, and secondly, of the major contribution that vascular access function makes to dialysis adequacy. Sodium removal is a third factor, which hitherto has not been widely perceived as influencing adequacy.

In clinical practice, absolute control of all of these variables is not possible in every dialysis session and some degree of variability in Kt is therefore inevitable. Continuous monitoring of dialysis adequacy allows physicians to ensure that an adequate dose of dialysis is being consistently delivered to chronic HD patients. Novel approaches to ensure this, such as variable treatment times guided by online assessment of clearance, warrant further investigation.

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Conflict of interest statement. None declared.

References


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