Implications of the Canada–USA (CANUSA) study of the adequacy of dialysis on peritoneal dialysis schedule

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Introduction

The Canada–USA (CANUSA) study of peritoneal dialysis [1] has increased awareness of the association between increased removal of small molecular weight solutes and improved patient survival. The data also suggest that patients who start continuous ambulatory peritoneal dialysis (CAPD) with little residual renal function are less well nourished and that a poor nutritional status is associated with decreased patient survival [2]. There is also a suggestion that patients with higher peritoneal transport, as defined by the peritoneal equilibrium test (PET) [3], have a decreased probability of survival [4]. These CANUSA-derived data suggest that dialysis treatment should be initiated earlier, that the total weekly clearance of small molecular weight solutes should be considerably higher than is current practice and that higher peritoneal transport is not a desirable feature for CAPD treatment. These suggestions are controversial [5,6]. There are concerns, in an incident dialysis population, about the relative value of clearance due to residual renal function and that due to peritoneal dialysis. Others are concerned that earlier initiation of dialysis may not be accepted by funding agencies and that the increased economic burden is not justifiable. Higher adequacy targets are not considered feasible for heavier patients with little residual function, and the increased cost of higher dialysate volumes may discourage some providers.

The objective of this review is to present the conclusions reached in the peer-reviewed publications from the CANUSA peritoneal dialysis study group [1,2,4] and to consider the controversy regarding the clinical inferences derived from those conclusions.

Methods

The methodology used in each of the three publications (Table 1) was reviewed and the results were summarized.

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<th>Subject</th>
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rate (GFR) defined as the average of urea and creatinine clearance. Daily clearances were converted to weekly by multiplying the daily values by seven. These estimates of adequacy of dialysis were determined when CAPD or CCPD training was completed and at 6 monthly intervals thereafter.

Estimates of nutritional status were obtained at the same intervals as for adequacy. These included the serum albumin concentration, the subjective global assessment (SGA) [8], protein catabolic rate (PCR) according to Randerson et al. [9] normalized to standard body weight (0.58/V) and percentage lean body mass (%LBM) from creatinine kinetics [10]. The statistical analyses are described in detail elsewhere [1].

**Results**

The relative risk (RR) of death was increased with increased age, dialysis in the USA, insulin-dependent diabetes mellitus, history of cardiovascular disease, lower serum albumin concentration, and worse nutritional status according to SGA and %LBM. The RR of death was decreased by 6% for a 0.1 greater weekly Kt/V and by 7% for a 5 l/1.73 m² greater weekly CCr.

**Conclusions**

Controlling for other independent variables, there is an association of greater weekly Kt/V and greater weekly CCr with a decreased RR of death. There was also an association of better nutritional status with a decreased RR of death.

**Prediction**

Data from the multivariate statistical analysis was used to create a mathematical model to predict survival at different levels of weekly Kt/V and weekly CCr. This model assumes that peritoneal and renal clearances are equivalent, and predicts the probability of survival, in this population, if total weekly clearances could be maintained at stable levels by increasing peritoneal clearance as renal clearance is lost.

The predicted 2 year survival probabilities are shown in Table 2. Over the range of adequacy studied, there was a progressive increase in the probability of survival with increased Kt/V and CCr.

**Clinical inference**

The theoretical constructs addressing adequacy of dialysis for CAPD [11–13] were reviewed recently [14]. These suggest that a weekly Kt/V of 2.0–2.2 would provide adequate dialysis. For a weekly Kt/V of 2.1, the predicted 2 year survival probability was 78% [1]. There are no theoretical constructs for CCr in CAPD. However, a 2 year survival probability of 78% was predicted by a CCr of 70 l/1.73 m². These were suggested as reasonable targets for CAPD [1]. The data also predict increased survival probability with increasing Kt/V and CCr.

**Controversy**

The target Kt/V selected as being reasonable is consistent with theoretical constructs [11–13]. Gotch has proposed [15] that the reference Kt/V for normal renal function be 12.96 weekly while the normal CCr is ~1000 l weekly. Expressed as a percentage of normal, a weekly Kt/V of 2.1 is 16% of normal and a weekly CCr of 70 l is only 7% of normal. It would appear logical to consider these to be reasonable targets but, when possible, to achieve greater Kt/V and CCr.

On the other hand, increased peritoneal dialysis dose for CAPD extracts a quality of life price in the time taken to perform exchanges and discomfort from larger dialysis volumes. Attainment of these targets with CCPD is associated with increased cost. Gotch argues, from the haemodialysis literature, that the RR of death does not decrease further with single-pool Kt/V >1.2 per dialysis for patients with thrice-weekly dialysis [15,16]. The equivalent Kt/V for CAPD is 2.0 per week. The choice of a CCr target of 70 l weekly in the CANUSA study reflects the greater relative contribution of residual renal function to CCr than to Kt/V. For patients with little residual renal function, Nolph et al. have reported equivalence between a Kt/V of 2.0 and a CCr of 60 l weekly [17]. Despite the convention of considering renal and peritoneal clearance equivalent, there are few data to support this concept.

**Summary**

A weekly Kt/V of at least 2.0 and/or a weekly CCr of at least 60 l are reasonable adequacy targets. Clearance from residual renal function and peritoneal clearance should be considered equivalent until there is evidence to reject this assumption. If higher clearances can be achieved without impairing patient quality of life or significantly increasing cost, this is desirable. Research addressing the equivalence of residual renal clearance with peritoneal clearance and clinical outcome research addressing the effect of higher adequacy targets should be given high priority.

**Renal function and nutrition at initiation of dialysis**

The second peer-reviewed publication from the CANUSA study group (Table 1) addressed the relationship between residual renal function and nutritional status at baseline [2]. It further evaluated the association between baseline nutritional status and patient survival.

**Table 2.** Predicted 2 year survival probabilities according to weekly Kt/V and CCr (l/1.73 m²)

<table>
<thead>
<tr>
<th>Kt/V</th>
<th>Survival %</th>
<th>CCr</th>
<th>Survival %</th>
</tr>
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<tbody>
<tr>
<td>2.3</td>
<td>81</td>
<td>95</td>
<td>86</td>
</tr>
<tr>
<td>2.1</td>
<td>78</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>1.9</td>
<td>74</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td>1.7</td>
<td>71</td>
<td>55</td>
<td>72</td>
</tr>
<tr>
<td>1.5</td>
<td>66</td>
<td>40</td>
<td>65</td>
</tr>
</tbody>
</table>
Methods

The residual renal function at initiation of CCPD was determined for the 680 patients enrolled in the CANUSA study [1] and expressed as renal Kt/V and as an estimate of GFR determined from the mean of renal urea and creatinine clearance. For each of renal Kt/V and GFR, three cohorts were created representing the upper, middle and lower thirds of residual renal function. For each tertile of residual renal function, nutritional status was expressed as the mean of serum albumin concentration, SGA, %LBM and nPCR. For several levels of each of these baseline nutritional estimates, the association with the actual survival probability was determined using the Kaplan–Meier method [18] and compared by the log-rank test.

Results

For weekly renal Kt/V, the mean value at initiation of continuous peritoneal dialysis was 0.71 [1]; one-third had values >0.89, one-third were 0.44–0.89 and one-third were <0.44. For weekly renal GFR, the mean value at initiation was 39.1 [1]; one-third had values >50, one-third were 25–50 and one-third were <251.73 m². The data for Kt/V and GFR defined tertiles are shown in Tables 3 and 4 respectively. For each of the estimates of nutritional status, higher initial residual renal function is associated with better nutritional status. For patients with initial serum albumin concentrations >35 g/l, 30–35 g/l and <30 g/l, the 2 year survival probabilities were 85, 75 and 64% respectively (P < 0.001; log-rank test). For those with initial %LBM >73%, 63–73% and <63%, the 2 year survival probabilities were 88, 81 and 65% respectively (P < 0.001; log-rank test). For those with initial nPCR values >1.02 g/kg, 0.9–1.02 g/kg and <0.9 g/kg, the 2 year survival probabilities were 83, 80 and 71% respectively (P < 0.001; log-rank test). These data are summarized in Table 5.

Conclusions

Lower residual renal function at the initiation of dialysis was associated with a worse nutritional status. In turn, worse initial nutritional status was associated with a decreased probability of survival.

Inference

Earlier initiation of dialysis would be associated with a better initial nutritional state and this would result in improved patient survival. If the adequacy target were a weekly total Kt/V of 2.0 or a weekly GFR of 601 (6 ml/min GFR or ~12 ml/min endogenous creatinine clearance), it would be illogical to allow the residual renal Kt/V or CCr to fall significantly below these values before initiating dialysis.

Controversy

Evidence supporting an earlier initiation of dialysis has been provided by Ikizler et al. [19] who reported a decrease in protein intake when CCr fell below 50 ml/min or 500 ml/week. For non-dialysed patients with a CCr <10 ml/min, the dietary protein intake was 0.54 g/kg body weight. Poor nutritional status is associated with worse outcome in both haemodialysis and peritoneal dialysis patients [20,21]. Bonomini has demonstrated superior survival among patients in whom haemodialysis was initiated early, and attributed the improvement to better nutritional status [22,23]. They reported an 88% 10 year survival among patients commencing haemodialysis therapy with CCr >10 ml/min compared with 55% for a group starting with a mean CCr of 4 ml/min [23]. Recently, Tattersall et al. reported increased morbidity among patients commencing dialysis with a weekly renal Kt/V <1.05 [24].

Arguments against an earlier start include the possibility of later initiation being a confounder which is linked to decreased access to medical care, poor patient compliance or suboptimal medical care. There may also be a starting time bias which gives an apparent rather than an actual survival advantage to those commencing dialysis earlier. There are no controlled

Table 5. Two year survival probabilities according to nutritional status at initiation of dialysis

<table>
<thead>
<tr>
<th>Albumin g/l</th>
<th>LBM %</th>
<th>nPCR g/kg</th>
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<tbody>
<tr>
<td>&lt;30</td>
<td>64%</td>
<td>&lt;63</td>
</tr>
<tr>
<td>30–35</td>
<td>75%</td>
<td>63–73</td>
</tr>
<tr>
<td>&gt;35</td>
<td>85%</td>
<td>&gt;73</td>
</tr>
</tbody>
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Log-rank P < 0.001 < 0.001 < 0.001

Arguments against an earlier start include the possibility of later initiation being a confounder which is linked to decreased access to medical care, poor patient compliance or suboptimal medical care. There may also be a starting time bias which gives an apparent rather than an actual survival advantage to those commencing dialysis earlier. There are no controlled
clinical trials demonstrating that earlier initiation does more good than harm, with peritoneal dialysis complications and increased glucose loads being two potentially harmful effects. In some countries, funding agencies may not reimburse for early initiation and thus there will be a significant increase in cost.

**Summary**

A reasonable solution would be to offer peritoneal dialysis to patients when the weekly renal $K_t/V$ is $< 2.0$ or the weekly estimate of GFR is $< 60 \text{l/minute}$ if there is concurrent evidence of malnutrition. This could be defined as a serum albumin $< 35 \text{g/l}$ or an nPCR $< 0.9 \text{g/kg}$. A study comparing an earlier initiation compared with conventional initiation should be considered high priority for a randomized clinical trial.

**Peritoneal membrane transport and patient survival**

The CANUSA study group have also addressed the association of peritoneal membrane transport with clinical outcomes and have reported these data in an abstract (Table 1) [4].

**Methods**

Patients enrolled in the CANUSA study of the adequacy of peritoneal dialysis [1] underwent a PET (3) at the completion of dialysis training and every 6 months thereafter. Patients with a 4 h dialysate:plasma (D/P) creatinine $> 0.65$ were considered high peritoneal transporters, while those with values $< 0.65$ were considered low transporters. This variable was added to the Cox proportional hazards model. The probability of technique and patient survival according to peritoneal transport status was determined using the Kaplan–Meier method [18]. The RR of technique and patient survival according to transport status was evaluated with the Cox proportional hazards method.

**Results**

The probability of 2 year technique survival was 79% among those with low transport compared with 71% among those with high transport. The RR of technique failure was 1.44 among those with high compared with those with low transport (95% confidence interval; 0.94–2.20). The probability of 2 year patient survival was 82% among the low transporters and 72% among the high transporters ($P = 0.04$; log rank test). The RR of death was 2.18 for high as compared with low transporters (95% confidence interval; 1.3–3.6). The RR associated with previously reported variables was unchanged [1].

**Conclusions**

Patients with higher than average peritoneal transport have an RR of 2.18 for death compared with low transporters. This is clinically important and statistically significant. There is a trend to an increased RR of technique failure among high transporters. Possible mechanisms include fluid overload from ultrafiltration failure, malnutrition from loss of proteins in the dialysate and adverse effects of increased glucose absorption.

**Inference**

Patients with higher than average transport should be observed for evidence of fluid overload and malnutrition. If present, the patient should be treated with cycling peritoneal dialysis or with haemodialysis. The former is preferable for those with high average transport in that shorter dwell times will decrease glucose absorption and improve ultrafiltration. Those with high transport may have better outcomes on haemodialysis.

**Evidence**

Other investigators have suggested worse outcomes among patients with high transport. Nolph et al. [25] reported that high transporters (as defined by Twardowski et al. [3]) had lower drain volumes, decreased nPCR, greater dialysate protein losses and lower serum albumin values than did those with low, low average and high average peritoneal transport. Heaf has demonstrated a detrimental association of high peritoneal transport with clinical morbidity [26]. This includes increased fatigue, nausea, pain, oedema, a symptom index and hospitalization. Recently, Davies et al. reported that a low $K_t/V$ and increased peritoneal membrane transport were both associated with an increased risk of death among CAPD patients [27]. On the other hand, the biological rationale for the increased morbidity and mortality associated with higher peritoneal membrane transport is speculative.

In addition, the finding of worse outcomes is counter-intuitive for those with high average transport in that these patients are predicted to have better outcomes by virtue of increased clearance of urea and creatinine.

**Summary**

Patients with high and high average peritoneal membrane transport should be monitored for evidence of fluid overload and malnutrition, the latter as previously defined. Transfer to cycling peritoneal dialysis should be considered. This should decrease glucose absorption and be associated with improved ultrafiltration. The decreased glucose uptake should also increase appetite and improve nutritional status. However, if fluid overload or malnutrition fail to improve, transfer to haemodialysis should be considered. Development of alternative osmotic agents should be a research priority.

**Discussion**

The three CANUSA studies reviewed [1,2,4] have addressed adequacy of dialysis [1], the association
between residual renal function at initiation of dialysis and nutritional status [2], the association between nutritional status at initiation of dialysis and patient survival [2] and the association between peritoneal membrane transport and both technique and patient survival [4].

These data suggest that increased clearance of urea and creatinine are associated with a decreased RR of death over the range of adequacy studied (Kt/V 1.5–2.3 per week; GFR 40–95 l/1.73 m² per week) [1]. They also suggest that earlier initiation of dialysis should be associated with better initial nutritional status and with improved patient survival [2]. The data also raise concerns regarding worse outcomes for patients with high and high average transport treated with CAPD, and suggest that cycling peritoneal dialysis with shorter dwell times might be preferable for these patients [4].

The suggestion, from the CANUSA study [1], that there is an increased survival advantage with urea clearance over the Kt/V range of 1.5–2.3 is consistent with the suggestion that longer and/or more frequent haemodialysis [28–30] might be associated with better clinical outcomes than that associated with conventional thrice-weekly haemodialysis. Protein intake, estimated from nPCR, has been suggested as an outcome for estimation of adequacy of dialysis [31]. As the Kt/V is increased, both in haemodialysis and peritoneal dialysis, the nPCR increases to an asymptote or plateau. For CAPD, this asymptote is reached at a weekly Kt/V of 3.0; for conventional thrice-weekly haemodialysis, the asymptote is at a weekly Kt/V of 6.0 [31,32]. Optimum dialysis is defined as the dose of dialysis (added to residual renal function) above which the incremental clinical gains are not worth the additional patient time or the additional cost. For CAPD, this dose probably lies between the current recommendation of a weekly Kt/V of 2.0 and the level of 3.0 suggested by the asymptote for nPCR.

The suggestion that dialysis be initiated earlier is not original. Bonomini and colleagues recommended this strategy in 1978 [22] but, despite demonstrating superior survival with an early initiation of dialysis, there has been little support for this approach. The CANUSA study data [2] have contributed to the renewed interest in earlier initiation of dialysis.

The CANUSA study has identified higher than average transport as associated with an increased RR of death [4]. This extends the observation of worse nutrition among high transporters made by Nolph and colleagues [25] and the increased morbidity observed by Heaf [26]. Recently, Davies and colleagues have reported increased mortality with increased peritoneal membrane transport [27]. This should stimulate clinical research to define the best treatment schedule based on transport status and to consider alternative osmotic agents.

However, the CANUSA study [1,2,4] used an observational, albeit prospective, rather than a randomized interventional research design. The data can be used to generate hypotheses which can be tested with a randomized clinical study design. Studies with patient survival as the clinical outcome will take several years to complete. Pending the results of these hypothesis-testing studies, it would be reasonable to implement the modified clinical strategies suggested by the CANUSA study results. These strategies are: (i) initiation of dialysis when the CCr is <12 ml/min if there is any evidence for malnutrition (e.g. serum albumin concentration <30 g/l or nPCR <0.9 g/kg body weight); (ii) during maintenance peritoneal dialysis, the total (renal and peritoneal) Kt/V should be >2.0 and the weekly CCr (renal GFR and peritoneal CCr) should be >60 l/1.73 m²; (iii) patients with high average and high transport according to PET should be treated with cycling peritoneal dialysis using shorter dwell times if there is evidence for fluid overload or malnutrition.

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