

## **Assessment of Peritoneal Dialysis Adequacy – Does it Impact on Patient Outcomes?**

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### **ABSTRACT**

The provision of adequate dialysis is important for the survival of Peritoneal Dialysis (PD) patients. Small solute clearance indices of urea and creatinine are widely used as markers of PD adequacy although several other factors are also known to affect optimal outcome in PD patients. Recently there is continued debate on the interpretation and precise prognostic value of small solute clearance in PD patients despite issuance of clinical practice guidelines and recommendations based on the solute clearance indices. We reviewed available literature on solute clearance indices in the assessment of PD adequacy and its association with patient outcome. Electronic data base such as the EMBASE, MEDLINE, OVID and Google internet search engines were used for the search as well as relevant textbooks. Several prospective cohort studies have been published on the effects of small solute clearance and other factors on mortality, morbidity and quality of life of PD patients. There are also some prospective controlled studies that used multivariate analysis to assess the relationship between solute clearance and other variables on patient outcomes. Randomised controlled studies however found that greater clearances did not lead to improved patient survival. Despite the continued debate on the interpretation and precise prognostic value of small solute clearance in PD

patients, dialysis recommendations based on the solute clearance have gained acceptance in clinical practice and a target dose of PD was recommended by National International organisations.

### **INTRODUCTION**

Adequate dialysis is defined as the dose of dialysis associated with acceptable morbidity and mortality, while optimum dialysis is defined as the level beyond which the added clinical benefit is not worth the additional patient effort or cost. <sup>1</sup> In the early days of dialysis, assessing adequacy was usually based on the clinical acumen of the physician to pick up signs and symptoms of inadequate dialysis such as nausea and vomiting together with laboratory parameters such as blood urea, creatinine and haematocrit levels. However, while the symptoms and signs are still relevant in this context, they have recognised limitations. First, their quantitative assessment is virtually impossible, secondly other causes of these symptoms and signs must be excluded and thirdly their appearance is usually late hence the opportunity for early detection of inadequate dialysis is usually missed.

Arkouche et al <sup>2</sup> showed that qualitative approach to assessing dialysis adequacy is not sufficient to predict the deleterious effects of under-

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dialysis. There is therefore the need for objective, quantifiable parameters to assess adequacy and early detection of under dialysis before the appearance of symptoms and signs. This would allow for comparison with other patient populations and correlation between the dialysis dose and clinical outcomes to be made.

Small solute clearance indices of urea and creatinine are widely used as markers of peritoneal dialysis (PD) adequacy. However several other factors are also known to affect patient outcome in dialysis patients. These include ultrafiltration, nutritional status, anaemia correction, mineral metabolism, control of lipids and other cardiovascular risk factors as well as acid base homeostasis.

For example, attention has recently been focused on the effect of ultrafiltration as a marker of PD adequacy and studies have shown that fluid removal is an independent factor affecting survival in PD patients.<sup>3</sup>

### **Urea Kinetic Modeling in Assessment of Peritoneal Dialysis Adequacy**

Results of the National Cooperative Dialysis Study (NCDS) and its re-analysis by Gotch and Sargent provided objective parameters for measuring adequacy of dialysis in haemodialysis (HD) patients.<sup>4,5</sup> They showed that indices derived from Urea Kinetic Modeling (UKM) were predictive of clinical outcome. Similarly, the study by Dyck et al of Mayo clinic and more recently the HEMO study attests to the significance of UKM in HD.<sup>6,7</sup> This UKM is a dimensionless measure of fractional clearance of body water for urea. It integrated efficiency of solute clearance (K), treatment time (t) and patient size (V) expressed as Kt/V. It has been validated and accepted as an index of adequacy in HD patients for many years. Attempts were made to extrapolate these same concepts in the assessment of PD patients. Teehan et al<sup>8</sup> were the first to show that measurement of blood urea nitrogen (BUN), normalized protein equivalent of nitrogen appearance (nPNA) and Kt/V provided a rational basis for uniform prescription of PD and allowed comparison between treatment centres as well as optimisation of dialysis and nutrition therapy. Reproducibility of the UKM in PD patients was also reported by Rodby et al.<sup>9</sup> The peak urea concentration hypothesis was later described by Keshaviah et al,<sup>10</sup> who found that a weekly Kt/V of 1.67 in CAPD was equivalent to a three times per week Kt/V of 0.86 for HD and for a three times per

week HD Kt/V of 1.3, with the corresponding equivalent weekly Kt/V of 2.0 for CAPD.

Several assumptions were made when applying UKM to PD; the rate of solute removal changes during dialysis in HD patients because the concentration of urea decreases during dialysis while in CAPD, clearance and solute removal stay about the same and are related in a linear fashion because the blood urea concentration is relatively constant. Urea achieves equilibration between dialysate and plasma at the end of the exchange in most CAPD patients, thus drain volume is analogous to urea removal (Kt).

Measurement of Kt/V in CAPD patients involves the measurement of both the renal and peritoneal urea clearances through the determination of the serum urea as well as the 24 h dialysate and urinary urea concentrations. Peritoneal Kt is calculated as the concentration of urea in the 24 hour dialysate sample divided by the serum urea concentration, while the renal Kt is calculated as the 24 hour urinary urea concentration divided by the serum urea concentration. The total Kt is normalized to total body water (V) which is obtained by using the Watson formula<sup>11</sup> which is based on the age, sex, height and weight of the patient. The value obtained is multiplied by 7 to give the weekly Kt/V.

There are versions of the Watson equation one of which is

$$\text{Men } V = 2.447 - 0.09516 * \text{age (years)} + 0.1074 * \text{height (cm)} + 0.3362 * \text{weight (kg)}$$

$$\text{Women } V = -2.097 + 0.1069 * \text{height (cm)} + 0.2466 * \text{weight (kg)}$$

Normograms have been prepared from these equations as well as computer based calculators.

The urea distribution volume (V) can also be estimated using a fixed percentage of body weight (60 percent of lean body weight in men, 55 percent in women). There are other equation based calculations for the determination of V such as the Hume formula and the Mellits- Cheek formula which is mostly used in children.<sup>12</sup>

The estimation of V has a great impact on the Kt/V equation and it can be inaccurate in some individual patients.<sup>13</sup> Overestimation of V could occur in obese patients while underestimation occurs in underweight patients. These inaccuracies must be taken into consideration when Kt/V targets are interpreted. To overcome these inaccuracies, most

investigators now consider the calculation of V based on the Watson formula as the method of choice rather than estimation as a fixed fraction of body weight.<sup>13</sup>

### **Creatinine Clearance in the Assessment of Peritoneal Dialysis Adequacy**

Creatinine clearance (CrCl) is used less often than UKM as an estimate of PD adequacy. National and international guidelines from the United States, Canada, Europe and the international society for peritoneal dialysis (ISPD) no longer recommend the use of CrCl as the surrogate measure of dialysis adequacy.<sup>13,14,15,16</sup> The exception is in patients on automated PD with low peritoneal solute permeability. In these patients, creatinine clearance will be more representative of the clearance of uraemic toxins.<sup>17</sup> Although it is acknowledged that monitoring the 24 hour dialysate and urine creatinine removal may be relevant because it is an estimation of muscle mass and may reflect phosphate clearance in these patients, certain limitations are known to be associated with CrCl, for example glucose interferes with the biochemical methods for the estimation of creatinine in the dialysate solution. There is controversy regarding the correct method for estimating residual glomerular filtration rate (GFR), though it is now recommended that the average of urea and creatinine clearances should be used.<sup>18</sup> Estimates of CrCl are usually normalised by body surface area (BSA). Creatinine clearance is expressed per 1.73m<sup>2</sup> body surface area and it has been suggested that the systematic error reported for V derived from anthropometric formulae would also apply to BSA derived in a similar manner.<sup>19</sup>

Peritoneal clearance is obtained by dividing the creatinine concentration in the 24hour dialysate (after being corrected for the interference of glucose in the measurement) by the serum creatinine concentration. The renal component is calculated as the average of urea clearance and creatinine clearance in the 24 hour urine. The value of the total clearance is corrected for 1.73m<sup>2</sup> body surface area (BSA) and then multiplied by 7 to get the weekly CrCl. The BSA is normally obtained using the formula of Du Bios which is given as.<sup>20</sup>  $A = W^{0.425} \times H^{0.725} \times C$ . where A is the surface area in square centimeters; H is the height in centimeters, W the weight in kilograms and C the constant, 71.84.

A chart has been plotted from this formula as well as computer based calculators so that the

approximate surface area may be determined at a glance.

### **Solute Clearance and Patient Outcomes in Peritoneal Dialysis**

Several prospective cohort studies have been published on the effects of small solute clearance and other factors on mortality, morbidity and quality of life of PD patients. Blake et al<sup>21</sup> reported a small increase in the probability of death for those with a weekly Kt/V <1.5 among 76 CAPD patients in Canada. Teehan et al<sup>22</sup> reported an increased survival in those with a weekly Kt/V value >1.89. De Alvaro<sup>23</sup> after following 102 CAPD patients for 12 months in a multicentre study in Spain reported that survivors had an average Kt/V of 2.0 compared to 1.7 for those who died. Lameire et al<sup>24</sup> reported a mean Kt/V of 1.89 in 16 patients who had survived 5 years on CAPD. Brandes et al<sup>25</sup> found that good clinical outcomes were associated with a mean weekly Kt/V value of 2.3 compared to 1.5 for poor clinical outcomes. Lo et al<sup>26</sup> in a study of 150 anuric PD patients, showed that Kt/V less than 1.7 was associated with greater mortality. In another prospective observational study on anuric patients in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), peritoneal Kt/V below 1.5 and creatinine clearance below 40 L/week/1.73 m<sup>2</sup> were associated with increased mortality.<sup>27</sup>

There are also some prospective controlled studies that used multivariate analysis to assess the relationship between solute clearance and other variables on patient outcomes. Maiorca et al<sup>28</sup> in an Italian study of 68 patients on PD reported that Kt/V less than 1.7, old age, peripheral vascular disease, dyslipidaemia, arrhythmia and initial low albumin were associated with poor outcome. Genestier et al<sup>29</sup> in a study of 201 patients found that lower Kt/V, cardiovascular disease, older age and diabetes were associated with worse survival.

The CANUSA study<sup>30</sup> was a large multicenter prospective study, performed among 680 incident CAPD patients in Canada and the USA with a mean follow up of 1.2 years per patient. The result showed a 6% reduction in the relative mortality risk for every 0.1 increase in Kt/V urea per week and 7% reduction for every 5 l/week/1.73m<sup>2</sup> increase in creatinine clearance; also, a Kt/V urea of 2.1 and a weekly creatinine clearance of 70 L/1.73 m<sup>2</sup> body surface area were both associated with a 78%

expected two year survival rate.<sup>30</sup> However in a re-analysis of the CANUSA Study, it was found that residual kidney function had confounded the previous analysis and its interpretation; residual kidney function and not dialysate clearance was associated with improved survival.<sup>31</sup>

Randomised controlled studies however found that greater clearances did not lead to improved patient survival. In the Adequacy of PD in Mexico (ADEMEX) study involving 965 patients, randomly assigned to continue their usual prescription (4 exchanges of 2L) versus a more aggressive dialysis prescription to reach a CrCl greater than 60 L/wk/1.73 m<sup>2</sup>, survival was found to be the same in both groups.<sup>32</sup> A subsequent randomised controlled trial from Hong Kong showed no difference in survival among three groups of CAPD patients with total Kt/V of 1.5 to 1.7, 1.7 to 2.0, and greater than 2.0 with minimal residual kidney function. However, patients with a Kt/V <1.7/week had more clinical problems, and higher erythropoietin requirements.<sup>33</sup>

### Solute Clearance Targets

There was an evolution of guidelines by various national and international organisations on the target dose of PD based on solute clearance parameters. The National Kidney Foundation (NKF) through the Kidney Disease Outcome Quality Initiative (KDOQI) issued the first guideline on the target dose of PD in 1997 which was revised in 2000, recommending a Kt/V greater than 2.0 and creatinine clearance (CrCl) greater than 60 L/wk/1.73 m<sup>2</sup> based largely on the data derived from the CANUSA study<sup>30</sup> as well as the Italian study.<sup>28</sup> The guidelines were later revised in 2006 after the release of data from the ADEMEX and Hong Kong studies,<sup>32, 33</sup> the findings of which supported the recommendation of lower weekly solute clearances. The current recommendation of the KDOQI is a minimum Kt/V of 1.7 in anuric patients and eliminated CrCl as a target.<sup>13</sup> This is similar to those recommended by the European Best Practice Guidelines (EBPG), even though the EBPG added a minimum peritoneal target for net ultrafiltration in anuric patients to be 1.0 liter/day.<sup>14</sup> The ISPD has also recommended that the total (renal + peritoneal) Kt/V urea should not be less than 1.7 at any time.<sup>16</sup>

### Creatinine Clearance or Kt/V

There are no data to suggest that one index is better than the other. For most patients, total weekly Kt/V

and CrCl are highly correlated.<sup>34</sup> However, up to 20% of patients will reach target with one adequacy measure, but not the other.<sup>35</sup> The reasons for these discrepancies are multifactorial, and include the degree of residual renal function present and its relative contribution to total Kt/V or CrCl. The latter is much more dependent on residual renal function. Another factor is the difference in peritoneal transport characteristics and the influence of patient size on normalization for V and also the BSA.<sup>1</sup> With the current guidelines, these arguments need not arise as most of them do not include the creatinine clearance measurement as a surrogate measure for PD adequacy.

## CONCLUSION

Despite the continued debate on the interpretation and precise prognostic value of small solute clearance in PD patients, dialysis recommendations based on Kt/V have gained acceptance in clinical practice with the issuance of practice guidelines by national and international organisations on the target dose of PD based on the Kt/V value achieved.

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