Peritoneal membrane characteristics and small solute clearance in chronic peritoneal dialysis patients

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ABSTRACT

The study was undertaken to analyze peritoneal membrane characteristics and small solute clearance in chronic peritoneal dialysis patients in an Australian peritoneal dialysis unit. Prospectively maintained database of end stage renal disease patients who commenced chronic peritoneal dialysis from January 2014 to December 2014, were analyzed retrospectively. Peritoneal equilibration test and the first ADEQUEST were done between 4 to 8 weeks of the commencement of peritoneal dialysis; second ADEQUEST was done 6 months after the first one. Twenty seven patients started chronic peritoneal dialysis during the study period, seven on continuous ambulatory peritoneal dialysis and twenty on automated peritoneal dialysis. On peritoneal equilibration test, high average transporters (52%) were the most common subgroup followed by high transporters (40%) and low average transporters (8%). None of the patients were low transporters. Weekly total Kt/V_{urea} was 2.57 ± 0.49 (1.63 - 3.73) at the time of commencement of peritoneal dialysis which decreased to 2.24 ± 0.45 (1.49 - 3.20) after six months. Weekly total creatinine clearance was 99.20 ± 27.59 (54.67 - 172.57), and 76.14 ± 21.34 (49.73 - 111.32) L/1.73 m^2 respectively at the start and 6 months after peritoneal dialysis. Monitoring of peritoneal membrane characteristics and small solute clearance helps the Nephrologists to individualize peritoneal dialysis prescription for their patients, however, the overall clinical and laboratory parameters should be taken into account whenever assessing the adequacy of peritoneal dialysis.

Keywords: peritoneal dialysis, small solute clearance, peritoneal equilibration test, adequacy of peritoneal dialysis

INTRODUCTION

Measurement of transport characteristics of peritoneal membrane helps nephrologists to choose the most appropriate peritoneal dialysis (PD) regimen for a given patient. Peritoneal equilibration test (PET) was first described by Twardowski et al in 1987.[1] Based on dialysate-to-plasma ratio of creatinine (D/P_{cr}) at 0, 2 and 4 hours and dialysate glucose at 4 hours compared to the dialysate glucose at time zero (D/D_0), peritoneal membrane can be classified into: High, high average, low average, and low transporters.[1-3]

Another important parameter to be measured in chronic PD patients is the clearance of small solutes, which can be measured in two ways: (1) weekly total (renal + peritoneal) urea clearance, as expressed by Kt/V_{urea} (2) weekly total (renal + peritoneal) creatinine clearance (CrCl).[4] This is done with a peritoneal adequest. The present study evaluates the peritoneal membrane characteristics and small solute clearance in chronic peritoneal dialysis patients in an Australian peritoneal dialysis unit.

METHODS

A retrospective analysis of prospectively maintained data base of end stage renal disease (ESRD) patients, who commenced chronic PD [either continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD)] from January 2014 to December 2014 in an Australian PD unit, was undertaken. The results of PET and weekly Kt/V_{urea} and weekly CrCl were analyzed. The study was approved by the institutional ethics committee.

PET and the first adequest were done between 4 to 8 weeks of the commencement of PD; second adequest was done 6 months after the first one. The protocol of this PD unit consists of measuring PET every two years, and adequest every 6 months after the first test.

PET was performed and analyzed as described by Twardowski et al.[1] Patients on CAPD were instructed to report to the PD unit with an overnight dwell (must be of 8 to 12 hours). A standardized four-hour PET procedure in the PD unit consists of the following sequential steps:

1. The overnight dwell is completely drained in sitting position over at least 20 minutes and drain volume is recorded.
2. A 2 liter of 2.5% PD solution is infused with the patient in a supine position over 10 minutes (infusion

rate approximately 200 ml/minute). The patient is instructed to turn from side to side every 2 minutes during the infusion to allow greatest contact of dialysate with the peritoneal membrane.

3. Using aseptic techniques, dialysate samples are drawn at time 0, 2, and 4 hour. Time 0 dwell occurs immediately after the dialysate is infused and time 4 hour dwell is at the completion of the 4 hour drain. To obtain the dialysate effluents, initially 200 ml of fluid is drained and mixed properly into the drain bag, and then 10 ml sample of the effluent is drawn from the medication ports, reinfusing the remaining effluent back into the peritoneal cavity. Effluent samples are sent for the analysis of urea, creatinine, and glucose.
4. A blood sample is taken when the 2 hour effluent sample is drawn, and the blood sample is sent for urea, creatinine, and glucose.
5. At 4 hours, the patient is completely drained allowing 20 minutes. An effluent sample is drawn as mentioned in step 3. The total drain volume is recorded.

Glucose interferes with the creatinine assay in the dialysate effluent significantly. To determine the correction factor, which is needed to correct for the falsely elevated creatinine level in dialysate samples, creatinine and glucose is measured in an aliquot of fresh 2.5 % glucose PD bag. Correction factor is calculated as follows:

$$\text{Correction factor} = \frac{\text{measured creatinine}}{\text{measured glucose}}$$

Calculations of D/P_{cr} (at 0, 2 and 4 hours) and D/P_0 glucose (at 2 and 4 hours) were done by PD Adequest software program. However, calculations can also be done manually by simple division of individual values.

The three calculated values for D/P_{cr} and two calculated values for D/D_0 are plotted on the standard creatinine and glucose PET curves (figure 1) respectively.[1] The transport category in which the values fall is noted.

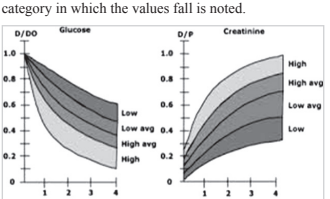

Figure 1: Twardowski curves: Transport status based on peritoneal equilibration test (PET)

Sometimes when the transport category determined by D/P_{cr} and D/D_0 glucose differs, D/P_{cr} is most commonly selected for membrane classification. The following steps describe the measurement of small solute clearance, with an adequest, in CAPD patients:

1. On the morning of the day before the clinic visit, patient is instructed to discard the first morning CAPD exchange. Drained effluent from each exchange after the first one is saved, including the morning exchange of the next day.
2. On the morning of the day before the clinic visit, patient discards the first urine and then starts collecting all the subsequent voids for exact 24 hours till next day.
3. Patient visits the clinic with the 24 hour timed collection of dialysate bags and urine, and their volume is measured.
4. An aliquot sample (1 % of the total volume) is drawn from each effluent bag, and the samples collected are mixed in another sterile container. A 10 ml sample of this mixed effluent is collected and sent to lab for urea and creatinine.
5. A 10 ml sample of urine is sent for urea and creatinine.
6. Remaining effluent and urine is disposed off.
7. Blood sample from the patient is taken for urea and creatinine.

Calculations of the weekly Kt/V_{urea} and weekly CrCl were done by PD Adequest software program. It is noteworthy that K is the urea clearance in volume/time, V is the volume of distribution of urea, which is equivalent to total body water, and t is the treatment time.

Calculations can also be done manually as follows:

Total weekly Kt/V

Weekly renal urea clearance (ml/week) = 7 x UV x Uu/Pu

$$\text{Weekly renal } Kt/V_{urea} = \frac{7 \times UV \times Uu/Pu}{V}$$

Weekly peritoneal urea clearance (ml/week) = 7 x DV x Du/Pu

$$\text{Weekly peritoneal } Kt/V_{urea} = \frac{7 \times DV \times Du/Pu}{V}$$

Total weekly Kt/V_{urea} = Weekly renal Kt/V_{urea} + Weekly peritoneal Kt/V_{urea}

[UV, 24 hour urinary volume in ml; Uu, urinary urea in unit/ml; Pu, plasma urea in unit/ml; DV, 24 hour drained dialysate volume in ml; Du, dialysate urea in unit/ml]

[V = Volume of distribution of urea pool i.e total body water, in ml (calculated by Watson formula)].[5]

For male,

V = + 2.477 + [0.3362 x wt (kg) + [0.1074 x ht (cm)] – [0.09516 x age (years)] = Litre (x 1000 = ml)

For Female,

V = - 2.097 + [0.2466 x wt (kg) + [0.1069 x ht (cm)] = Litre (x 1000 = ml)

[Note: minus sign]

[wt, actual body weight in kg; ht, height in cm]

Total weekly CrCl

Weekly renal CrCl normalized to 1.73 m2 body surface area (BSA) = 7 x UV x Ucr/Pcr x 1.73/BSA

Weekly peritoneal CrCl normalized to 1.73 m2 body surface area (BSA) = 7 x DV x Dcr/Pcr x 1.73/BSA

Total weekly CrCl normalized to body surface area = weekly renal CrCl + weekly peritoneal CrCl (ml/BSA).

[UV, 24 hour urinary volume in ml; Ucr, urinary creatinine in unit/ml; Pcr, plasma creatinine in unit/ml; DV, 24 hour drained dialysate volume in ml; Dcr, dialysate creatinine in unit/ml]

Body surface area (BSA) is calculated by DuBois and DuBois method.[6]

$BSA = 71.84 \times W^{0.425} \times H^{0.725} \times 10^{-4}$

[W, actual body weight in Kg; H, height in cm]

Data were expressed as percentage and mean ± standard deviation (SD). Statistical analysis were done using SPSS software version 16.

RESULTS

Twenty seven ESRD patients started chronic PD during the study period, seven on CAPD and twenty on APD. The baseline characteristics of the patients are shown in Table 1.

PET was performed in twenty five patients within 4-8 weeks after starting PD. PET was not performed in two patients within the study period because of peritonitis episodes in this time period which can have acute and chronic effects on the peritoneal membrane. It is recommended to wait for at least 1 month before performing a PET after a peritonitis episode.

Table 1: Baseline characteristics of the patients on chronic peritoneal dialysis (27 patients)

Characteristics	Mean ± SD / N (%)
Age (years)	56 ± 14.6 (range 18 to 82)
Sex (M/F)	21/6 (77.8/22.2)
BMI	24.9 ± 3.2 (range 19.1 to 32.0)
Primary renal disease: Diabetes mellitus Glomerulonephritis Hypertension Miscellaneous Unknown	 8 (29.6) 7 (26) 3 (11) 7 (26) 2 (7.4)
CAPD/ APD	7/20 (26/74)
Patients who selected PD as a first mode of RRT Patients who were transferred from Hemodialysis	23/4 (85/15)

Table 2 illustrates the distribution of peritoneal membrane characteristics among the study population. High average transporters (52%) were the most common subgroup followed by high transporters (40%) and low average transporters (8%). None of the patients were low transporters.

Table 2: Membrane transport characteristics of the chronic peritoneal dialysis patients (25 patients)

Membrane Transport	N (%)
High (H)	10 (40)
High Average (HA)	13 (52)
Low Average (LA)	2 (8)
Low (L)	0 (0)

Weekly Kt/V_{urea} and CrCL, using Adequest, were performed at the time of PET procedure in twenty five patients after 4-8 weeks of starting PD therapy. Second Adequests were done in eleven of these patients during the study period, after six months of the first test. Table 3 demonstrates the clearance tests at the commencement and six months after PD therapy.

DISCUSSION

Determination of the peritoneal membrane characteristics helps in tailoring peritoneal dialysis prescription in chronic peritoneal dialysis patients. High transporters achieve rapid and complete equilibration of small solutes, but quickly lose their osmotic gradient and achieve poor ultrafiltration. They are, therefore, good candidates for APD regimens that use shorter dwell times. In contrast, low transporters benefit more on modalities allowing for

Table 3 : Small Solute Clearance of the chronic peritoneal dialysis patients

Characteristics	Mean ± SD (range)
First Adequest test (25 patients)	
Weekly total Kt/V_{urea}	2.57 ± 0.49 (1.63 - 3.73)
Dialysate Kt/V_{urea}	1.52 ± 0.23 (1.24 - 2.22)
Residual Kt/V_{urea}	1.05 ± 0.48 (0.0 - 2.27)
Weekly total CrCl (L/wk/1.73 m^2)	99.20 ± 27.59 (54.67 - 172.57)
Dialysate CrCl	44.00 ± 6.02 (31.34 - 54.67)
Residual CrCl	55.60 ± 27.32 (0.0 - 128.07)
Second Adequest test (11 patients) (6 months after the first Adequest test)	
Weekly total Kt/V_{urea}	2.24 ± 0.45 (1.49 - 3.20)
Dialysate Kt/V_{urea}	1.43 ± 0.61 (0.73 - 2.68)
Residual Kt/V_{urea}	0.81 ± 0.50 (0.0 - 1.70)
Weekly total CrCl (L/wk/1.73 m^2)	76.14 ± 21.34 (49.73 - 111.32)
Dialysate CrCl	38.26 ± 19.08 (18.26 - 84.16)
Residual CrCl	37.88 ± 23.83 (0.0 - 80.34

longer dwell times such as CAPD, as they generally have reduced solute clearance and sustained ultrafiltration. Low transporters may sometimes need to be transferred to hemodialysis if they continue to have features of inadequate dialysis even on long dwell CAPD. Patients with high average or low average transport category can be put on either APD or CAPD.[7]

The CANUSA (CANADA and USA) study in 1996 was the land mark trial which demonstrated the effect of small solute clearance on survival.[8] It was a prospective observational study and enrolled 680 CAPD patients who were on four daily exchanges of 2 L bag. The study showed that a decrease of 0.1 unit total Kt/V_{urea} per week was associated with a 5% increase in the relative risk (RR) of death, for Kt/V_{urea} between1.5 to 2.3. A decrease of 5 L/1 .73 m^2 total CrCl per week was associated with a 7% increase in the RR of death. A total weekly Kt/V_{urea} of 2.1 and total weekly CrCl of 70 L/1.73 m^2 were each associated with an expected 2-yr survival of 78%.

CANUSA study was based on the assumption that renal and peritoneal clearances are equivalent in influencing outcomes. The results of the study were interpreted as indicating that increase in total solute clearance would result in improved survival. Because the renal component of the small solute clearance decreases with time, it was assumed that if small solute clearance could be increased with enhanced peritoneal clearances then outcomes would be improved.

Based on the CANUSA study and other similar observational studies[8-11], Dialysis Outcomes Quality Initiative (DOQI) guidelines in 1997 recommended that for CAPD, the delivered PD dose should be a total Kt/V urea of at least 2.0 per week and a total creatinine clearance (CCr) of at least 60 L/wk/1.73 m^2.[12] However, this was not easily achievable in many patients.

The reanalysis of CANUSA study in 2001 showed that it is the residual renal function that determines survival and not the peritoneal clearance.[13] It was observed that there was a 12% decrease in the relative risk (RR) of death for each 5 L/wk per 1.73 m2 increment in renal clearance, but there was no association with peritoneal clearance.

The study suggested that residual renal function is biologically more important than the peritoneal clearance partly because of better clearance of middle and larger molecular weight uremic toxins by renal clearance.

What is the effect of increasing the peritoneal clearance (beyond a standard minimum prescription) on survival in chronic PD patients, as residual renal function (renal clearance) declines with time? This question was answered by two prospective randomized controlled interventional trials: ADEMEX (ADEquacy of PD in MEXico) and Hong Kong multicentre study.In the ADEMEX study (2002) [14], 965 chronic PD patients were enrolled who were on four daily exchanges of 2 L and with peritoneal creatinine clearance of < 60 L/wk/1.73m^2, irrespective of their residual renal function. They were randomized in 1: 1 ratio to control group and intervention group. Patients in the control group continued with their original PD prescription of four daily exchanges of 2 L (mean peritoneal creatinine clearance 45 L/wk/1.73m^2). However, PD dose was increased (by increasing exchange volume to 2.5 or 3 L and/or the number of exchanges to 5 per day by use of a device) in the intervention group to achieve peritoneal clearance value of 60 L/wk per 1.73 m^2.

Despite differences in small solute clearances, patient survival was similar for the control and intervention groups over 2 year period. Overall, the control group and intervention group exhibited a 1-yr survival of 85.5% and 83.9 % and a 2-yr survival of 68.3% and 69.3 % respectively. ADEMEX study suggested that once a certain level of peritoneal clearance is achieved further increase in peritoneal small solute clearance does not improve survival. However, the authors warned that their study should not be taken as a reference to pay poor attention to peritoneal clearance. Though survival is not affected by enhancement of peritoneal small solute clearance beyond a certain minimum target, higher peritoneal clearances might be necessary in some patients for the overall well being.

The HONGKONG multicentre study (2003) [15] gave similar results to ADEMEX study. 320 new CAPD patients, who were on three daily exchanges of 2 L and with renal Kt/V < 1, were randomized into three groups with different total Kt/V_{urea} targets: group A, 1.5 to 1.7; group B, 1.7 to 2; and group C, greater than 2. PD prescriptions were modified accordingly. Total Kt/V_{urea} was significantly different between groups and the difference was contributed by peritoneal Kt/V only. However, the 2 year patient survival was 87.3 %, 86.1%, and 81.5% for study groups A, B, and C respectively and the difference was not statistically significant. The authors recommended that the minimal total Kt/V_{urea} target should be 1.7 and patients should be kept at total Kt/V_{urea} between1.7 to 2. They suggested that while one should not refrain from increasing the dialysis prescription to higher Kt/V_{urea} level in order to control other clinical parameters, deliberate maintenance of Kt/V_{urea} above 2 without these indications may not be necessary.

Based on these studies the ISPD guidelines in 2006 recommended that the total (renal + peritoneal) Kt/V_{urea} should not be less than 1.7 at any time. That means, in anuric patients (24 hour urine < 100 ml), peritoneal Kt/V_{urea} has to be above 1.7.[16]

The 2006 ISPD guidelines as well as the ADEMEX and Hong Kong multicentre study emphasize that adequacy of peritoneal dialysis should not be taken as a synonymous to small solute clearance (which was the widely held belief in 1990s). Adequacy of dialysis should involve not only the peritoneal and renal clearance but the overall clinical assessment of patient including hydration status (maintaining euvolemia), appetite and nutritional status, energy level, hemoglobin concentration, responsiveness to erythropoietin therapy, electrolytes and acid–base balance, calcium phosphate homeostasis, and blood pressure control.[14-16] Most of the patients in Asia, including in the Hong Kong multicentre study, do only three manual exchanges of 2 L per day and have a good survival rate.[17, 18] In Nepal, CAPD as a mode of RRT is being utilized by few patients and they do three 2 L manual exchanges per day.[19, 20] However, determination of peritoneal membrane characteristics and measurement of small solute clearance is not done.

Currently dialysis centers in Nepal provide 2 hemodialysis sessions (of 4 hour each) per week to the ESRD patients at a cost of about 250 USD per month, under the government reimbursement policy. Nepal government reimburses the same amount for peritoneal dialysis, however, that covers only the cost of 2 exchanges per days. Patients on CAPD in Nepal pay for the third bag from their pocket. Monitoring of small solute clearance in Nepalese CAPD patient is necessary to check whether we are providing a minimum total weekly Kt/V_{urea} of 1.7, as some patients may need 4 exchanges per day. Furthermore, such data from Nepal would be a supporting scientific evidence for Nepalese Nephrologists to ask the Nepalese government to reimburse for at least three bags per day, if any. Of course, such data on small solute clearance is also needed in hemodialysis patients to advocate for 3 hemodialysis sessions per week, at least in selected patients, if not in all. However, that discussion is not within the scope of present article.

In conclusion, monitoring of peritoneal membrane characteristics and peritoneal and renal small solute clearance helps the Nephrologists to individualize the PD prescription for their patients, however, the overall clinical and laboratory parameters should be taken into account whenever assessing the adequacy of peritoneal dialysis.

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