Adequacy in dialysis: intermittent versus continuous therapies

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INTRODUCTION

In the early 1960s and 1970's, clinical acumen of the nephrologist and routine laboratory parameters were the only measures available to estimate the dose of dialysis. Much progress has been made since the days of National Cooperative Dialysis Study (NCDS), which for the first time looked at this important issue in a controlled manner[1,2]. Though the NCDS was a landmark study in more ways than one, it made no effort to determine if higher levels of KT/V (> 1.0) were associated with further improvement in survival.

More recently, the USRDS in it's latest report has shown a steady and progressive decline in one year mortality for all dialysis patients prevalent at the beginning of each year from 1988 to 1992 despite an aging population and a higher number of new diabetic patients, factors which increase comorbidity and mortality[3]. A retrospective analysis of 13,473 patients comparing patient outcome to dialysis intensity reported a lower patient survival with a urea reduction ratio of less than 60% [4]. Several other studies showed improvement in patient survival with increased dialysis dose[5-9].

In peritoneal dialysis, although the prospective, cohort multicenter CANUSA study showed a relationship between mortality and Kt/V, the survival was linked to the residual renal function (which changed over time) rather than the peritoneal clearance (which did not change)[10]. Therefore although better peritoneal clearance has not been shown to lead to better survival, it is widely believed that the observations from the hemodialysis population can safely be extrapolated to peritoneal dialysis too.

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THE RELATIONSHIP OF DIETARY PROTEIN INTAKE TO WEEKLY KT/V UREA IN CONTINUOUS AND INTERMITTENT THERAPIES

Intermittent therapies need a higher Kt/V urea to maintain a given protein intake:

Adequacy of dialysis remains inextricably linked to nutritional status. Under-dialysis is associated with malnutrition in dialysis patients. Since in most underdialyzed patients a low BUN may be reflective of a poor protein intake, evaluation of protein intake and adequacy must be linked. In patients with neutral nitrogen balance, nPNA represents an index of protein intake. There is a curvilinear relationship between the amount of dialysis (as measured by Kt/V urea) and protein intake (as measured by nPNA) and varies between intermittent (hemodialysis) and continuous therapies (peritoneal dialysis)[11]. Concerns have been raised about the mathematical coupling between nPNA and Kt/V since both are derived from the product of dialysate urea nitrogen concentration and drain volume and both are related to BUN concentration[12]. However the curvilinear relationship between these two variables, differences between the relationship of continuous and intermittent therapies and plateaus of nPNA at high Kt/V urea levels support a physiologic component to the relationship. More dialysis presumably increases appetite thus increasing nPNA to a plateau at which supposedly uremic inhibition of appetite is minimized[11]. Providing further support to this argument are the studies by Lindsay et al which show that more dialysis stimulates appetite rather than the possibility that better appetites result in higher BUN thus prompting nephrologists to prescribe more dialysis[13]. At weekly Kt/V urea values from 1.5 to 3.0, nPNA values with CAPD are usually higher than those with hemodialysis (see below). In other words, patients on continuous therapies achieve a higher nPNA for the same level of Kt/V as compared to patients who are on intermittent therapies.

Several hypotheses have been put forward to explain the variable relationship between Kt/V and

nPNA. Scribner et al in 1971[14] proposed their *middle molecule* (MW 500-5000 Dalton) hypothesis. This hypothesis was based on the observation that apparently underdialyzed chronic peritoneal dialysis patients failed to develop symptomatic peripheral neuropathy (a principal indicator of underdialysis). This was thought to be due to the superior ability of the more permeable peritoneal membrane to effectively remove middle molecules despite a lower small solute clearance when compared with hemodialysis. It has also been reported that with increasing Kt/V the increase in PCR is larger in CAPD than hemodialysis patients[15,16]. This may imply that middle molecules may play an important role in uremic anorexia and are more efficiently removed by CAPD than hemodialysis. This proposed better removal of middle molecule «toxins» suppressing appetite may therefore be one of the determinants of different relationship between Kt/V urea and nPNA in peritoneal dialysis vis a vis hemodialysis.

Keshaviah however, analyzed data on mass transfers characteristics of peritoneal and HD membranes and refuted the contention that CAPD removal of middle molecules is superior to hemodialysis[17]. Proposing his *peak concentration hypothesis* he observed that the major difference between intermittent therapy like hemodialysis and continuous therapy like CAPD is that body levels of various uremic toxins remain constant in CAPD whereas in hemodialysis the levels have a saw tooth profile with troughs and peaks. Urea nitrogen concentration is assumed to be a surrogate marker of a small molecular weight appetite suppressant. Control of peak serum urea nitrogen concentrations is therefore important for maintaining appetite and protein intake. Since the uremic toxicity (according to the hypothesis) is related to the amount of time that uremic toxin(s) concentrations are above the toxic levels rather than to the time averaged concentration (TAC) of the toxin(s), patients on intermittent treatments require higher weekly urea clearances to maintain peak values at or below the steady state levels of CAPD at the same level of urea generation. Alternatively, at the same weekly urea clearance, the higher peak concentrations in hemodialysis may be associated with appetite inhibition[18]. It is apparent that with intermittent therapies, as the therapy becomes more frequent, the required Kt/V decreases relative to the peak control. Since continuous therapies are the extreme end of this frequency spectrum, they require the lowest Kt/V per day to achieve a given level of peak control.

There are some other relevant issues with intermittent dialysis. When dialyzed blood returns to the body pool it dilutes the dialyzable pool of toxins itself thus affecting the efficiency of dialysis by decreasing the solute gradient. Since solute removal is the product of clearance and solute concentration, there is an exponential fall in solute concentrations during hemodialysis (the sharp fall in BUN during a dialysis session may result in approximately 70% reduction of efficiency of dialysis by the end of session). As a result the true average concentration is always lower than the mean of pre and post dialysis BUN. The more frequent the dialysis the lesser the deviation of the true average concentration from the mean concentration. In other words the less the BUN changes during the dialysis the more efficient the dialysis becomes. Therefore a negative tradeoff of rapid intermittent therapy is the drop in dialysis efficiency as the session progresses.

Also, even though urea is the most diffusible organic solute accumulating in patients with renal failure, the body does not behave as a single pool with regard to diffusion of urea. A disequilibrium develops between various body compartments during hemodialysis. This is of measurable magnitude and depends on the intensity of the dialysis expressed as K/V[19]. Solute disequilibrium thus tends to further hamper dialysis efficiency by worsening the problem created by dilution by reducing solute gradient across the cell membrane. Solute disequilibrium may also be caused by cardiopulmonary recirculation (that depends on ratio of dialyzer clearance and systemic blood flow) during hemodialysis. Interestingly, the mass transfer of middle molecules from the intracellular compartment to the blood is restricted with urea disequilibrium between different body compartments thus at least theoretically limiting the removal of middle molecules in HD as compared to PD.

ADEQUACY TARGETS FOR CONTINUOUS AND INTERMITTENT THERAPIES[20,21]

a) CAPD.
b) CCPD.
c) NIPD.
d) Thrice weekly HD.

The Dialysis Outcomes Quality Initiative of the National Kidney Foundation has published clinical practice guidelines for intermittent and continuous therapies based on a number of cohort studies and theoretical constructs.

a) CAPD

For a continuous therapy like CAPD the guidelines recommend a minimal delivered dialysis dose

target to be total Kt/V urea of 2.0 per week; the minimum weekly target total creatinine clearance (CCr) should be 60L/1.73m^2. In the event there is discordance in achieving these targets, the guidelines recommend Kt/V urea as the immediate determinant of adequacy owing to the fact that it directly reflects protein metabolism and is less affected by extreme variations in residual renal function (RRF). However, as a note of caution, the guidelines recommend a search for a cause for this discrepancy and a careful watch for symptoms and signs for under dialysis. At present there is not enough evidence to discriminate between adequate and optimal dialysis (dialysis dose above which the incremental clinical benefit does not justify the patient burden or financial costs).

b) CCPD

For CCPD the guidelines recommend a weekly total Kt/V urea of at least 2.1 and a weekly total creatinine clearance of 63L/1.73m^2. In comparison to CAPD this therapy is deemed to be less continuous in nature (although some variations of CCPD with diurnal exchanges of less duration than the nocturnal exchange of CAPD may be considered to be equal to CAPD). It has been assumed that requisite delivered dose for CCPD would be intermediate between CAPD and NIPD.

c) NIPD

Similar to CCPD, these recommendations are based on opinion rather than evidence. In theory there is at least 8% difference between CAPD and NIPD. This difference is derived from the fact that for intermittent hemodialysis a 200% increase in clearance is required to achieve the same solute removal as in continuous dialysis (Kt/V urea of 4.0 in hemodialysis and 2.0 in CAPD) while holding protein intake constant. The authors of the recommendations therefore assumed that the delivered dose of NIPD would need to be 8% higher than the CAPD dose (108% of 2.0 = 2.16 - rounded up to 2.2).

d) Thrice a week hemodialysis

In HD, for both adult and pediatric hemodialysis patients, a minimum Kt/V of 1.2 or a minimum URR of 65% is recommended (URR varies with ultra filtration). Though adequate evidence exists for a minimum dose of HD, DOQI does not define what constitutes optimal dose for hemodialysis patients. Furthermore, as in all other forms of dialysis, the prescribed dose of dialysis may differ from the dose actually delivered. Physical factors like access re-circulation etc. may affect urea clearance. This together with reduction in treatment time and laboratory and sampling errors may impact on delivery of the prescribed dose of dialysis. In the NIH Hemodialysis study[22] (which is rigorously controlled in terms of dose prescription and measurement) the 90% confidence limit for the single pooled Kt/V of 1.3 is 0.10. Also the 90% confidence limit for urea reduction ratio (URR) is 4%. In view of these findings the DOQI recommends that the prescribed minimum targets for Kt/V and URR be 1.3 and 70% respectively.

ADEQUACY TARGETS AND PATIENT SURVIVAL

Comparison of survival between intermittent and continuous therapies (e.g. CAPD and HD) is complex and a number of confounding variables affect the final analysis. A prospective comparison of these therapies adjusting for case mix (disease severity, comorbidity), dose of dialysis and nutritional state has not yet been done. It is not surprising therefore that conflicting data exists in the literature when adequacy of dialysis is compared to clinical outcomes[23-28]. These studies are limited by small sample size resulting in inadequate statistical power, use of univariate rather than multivariate analysis and insensitive clinical outcomes.

Canada-USA (CANUSA) study was one of the first large multicenter prospective cohort studies to evaluate the relation ship between adequacy and mortality in continuous peritoneal dialysis patients[10]. It looked at the relation between adequacy of dialysis and modeled mortality in 680 incident peritoneal dialysis patients using the Cox proportional hazards model. A decrease of 0.1 unit of Kt/V week was associated with a 5% increase in relative risk (RR) of death; a decrease of 5L/1.73m^2 creatinine clearance per week was associated with a 7% increase in the RR of death. The study reported an expected 2 year survival of 78% with a sustained weekly Kt/V value of 2.1(the corresponding figures for weekly creatinine clearance being 70 L/week/1.73m^2). Within the dialysis doses studied in this analysis, higher adequacy targets (Kt/V and CCr) were associated with improved survival. It must be realized however that patients in this study were in the initial 2 years of dialysis and thus maintained significant RRF. Also, the expected probabilities of 2 year survival were based on the inherent assumption that renal and peritoneal clearances are equal and that increased pe-

ritoneal clearance will compensate for the loss of RRF. Despite these caveats this study provided convincing evidence of a positive link between adequate dialysis and patient survival in patients on continuous dialysis.

Keshaviah et al[29] compared survival between HD and PD with the patient population matched for dose of dialysis. Utilizing the CANUSA database for PD population (N = 680, 14 center, 2 year follow up) and RKDP, Minneapolis database for HD population (N = 1051, 6 year follow up), the authors compared 2 year patient survival in both diabetic and non diabetic groups using multivariate analysis. Three age groups (< 45, 46-60, > 61) and two levels of Kt/V (mid Kt/V: 1.0-1.5 per HD and 1.7-2.1 per week in PD; high Kt/V: > 1.5 per HD and > 2.1 per week for PD) were studied. Their results demonstrated a higher survival in the higher Kt/V patient groups, both for both HD as well as PD, although no difference in comparable survival between HD and PD was observed in these dose- matched patients. Results of these two large databases highlight the fact that though more dialysis is associated with a better survival[10,29], yet when adjusted for dialysis dose comparisons of survival between HD and PD become insignificant [29].

INCREMENTAL DOSING OF CONTINUOUS AND INTERMITTENT THERAPIES

The healthy start concept

The high morbidity and mortality of patients with ESRD has highlighted the importance of pre ESRD care. It is paradoxical, however, that when patients are on dialysis, all attempts are made to achieve maximum solute clearances, while in the pre ESRD state their renal solute clearances often deteriorate to levels far below the adequacy targets for chronic dialysis. There is now adequate evidence that the level of residual renal function and nutritional status at initiation of dialysis are independent predictors of outcome[30,31] and in patients in whom dialysis is initiated late, it fails to reverse the adverse effects of uremia on a patient's nutritional status dialysis[32]. Both in North America and Europe, the weekly Kt/V urea levels at the time of initiation of dialysis are far below the minimum adequacy targets for chronic dialysis[10,30] (weekly Kt/V urea of 0.71 and 1.05 respectively).

Since protein intake declines spontaneously with progressive uremia[33] and nPNA (determined by urea kinetic modeling) at the time of initiation of dialysis is inversely related to subsequent morbidity and mortality on dialysis[34,35] a case can be made for an earlier initiation of dialysis. However the level of renal function at which dialysis should be initiated has been the subject of debate[20,36,37]. Until a randomized controlled trial answers the question, a strategy needs to be formulated for timely initiation of dialysis. Clearly dialysis should be initiated before irreversible consequences of uremia develop. Based on the recognition that nPNA represents a surrogate marker of nutrition in dialysis patients, the Dialysis Outcomes Quality Initiative (DOQI) of the National Kidney Foundation proposes initiation of incremental dialysis before the nPNA declines below 0.8gm/Kg std. wt./day[2]. Since there is now some evidence that the relationship between Kt/V urea and nPNA in CAPD patients is similar to pre dialysis patients[38], the use of adequacy targets for small solute clearances for CAPD as targets for initiation of chronic dialysis as proposed by DOQI seems scientifically reasonable. Therefore, incremental chronic dialysis should be initiated when the weekly renal Kt/V urea falls below 2.0 (assuming a TBW of 35L this is equivalent to a urea clearance of 7 ml/min/1.73m^2, a creatinine clearance of 14 ml/min/1.73m^2 or a mean of renal urea and creatinine clearance of 10.5 ml/min/1.73m^2). Over time the dialysis dose should be augmented to keep the combined renal and dialytic weekly Kt/V urea at around 2.0[20].

Incremental dosing for PD and intermittent HD

In the above context it is recommended that the dose of dialysis needs to be increased with the decline of residual renal function in an effort to maintain combined renal weekly K_r t/V urea and dialytic clearance at 2.0. It has been a subject of debate as to whether renal and dialytic small solute clearances can be considered equivalent. Despite evidence cited above[38], this controversy still exists. In the CANUSA study, the modeled mortality doubled in the second year suggesting a possible decline in the renal component of total clearance. It appears understandable therefore to consider incremental chronic dialysis once K_r t/V (renal Kt/V) urea falls below 2.0 in order to preserve a patient's nutritional status. Using mathematical modeling, equilibrated delivered dose (eK_d t/V) curves based on kinetic criteria for equivalency between intermittent and continuous dialysis have been generated and help in calculating the dose of incremental dialysis necessary to achieve a weekly K_T t/V (total urea clearance or total Kt/V) urea of 2.0[36]. Since both PD and renal clearances are continuous the dose of incremental dialysis necessary can be calculated as 2.0 - K_r t/V urea.

For intermittent HD the equilibrated, delivered and normalized HD dose, eK_d t/V, necessary to ensure a weekly K_T t/V urea of 2.0 is based on an eK_d t/V of < 2.0 and depends on RRF and the frequency of dialysis. On the basis of this modeling it appears that either HD or PD can provide incremental dialysis with minimal interruption of patient lifestyle. For example at the outset, a single overnight exchange or one HD weekly would be able to restore the weekly K_T t/V urea to 2.0. Though there is a debatable risk of infection and / or patient 'burnout' with this approach reduced death risk and improved nutrition are positive tradeoffs with this approach.

Using urea kinetic modeling, Keshaviah et al[39] have also demonstrated the feasibility of compensating for declining RRF by appropriate titration of dialytic dose to maintain a constant Kt/V of 2.0 and a BUN concentration that matches the value at the start of dialysis. Assuming an average rate of decline of RRF (calculated from the literature), authors have shown that for the first 18 months only nocturnal exchanges are needed in the average patient after the initiation of a continuous therapy like PD. Subsequently, incremental exchanges can be introduced in the dialysis regimen without significant retraining.

For those undergoing intermittent therapy like HD, once a week dialysis may be sufficient for the first five months following initiation of dialysis. The duration of dialysis may however need readjustment however to keep pace with the decline in the RRF. However, in order to avoid wide biochemical swings, twice a week HD may be a better option when using an incremental approach [39]. Since with CAPD it is possible to achieve a Kt/V of 2.0 for almost 18 months and additional exchanges can be easily added to the regimen, a 'healthy incremental start' may be easier to achieve with PD than HD[39].

ADEQUACY CONSIDERATIONS FOR DAILY OR NOCTURNAL HD

Time averaged concentration (TAC) versus Time averaged deviation (TAD)

From the above discussion in relation to mass transfers and disequilibrium it may become obvious that enhancing dialysis dose either by increasing clearance or prolonging time on dialysis operates on law of diminishing returns. However, the efficiency of dialysis can be further improved by considering another vital component of dialysis prescription i.e. the frequency of dialysis. In other words, the total weekly Kt/V can be adjusted by manipulating the schedule of treatments as well as K and t.

In 1988, Lopot and Valek[40] while commenting on the unphysiology of infrequent hemodialysis, presented the concept of TAC versus TAD or Time Averaged Deviation of blood urea. TAC or Time Averaged Concentration is calculated as the area under the curve divided by the total time of investigational interval, whereas TAD is determined by measuring the area of deviations from the TAC and dividing it by total time of observation. TAC represents an inadequate measure of dialysis adequacy. TACs of several short dialyses as compared to one long hemodialysis (once a week) may be the same but the peak values of blood urea and other toxins may be undesirably high in the latter (in other words TAD will be extremely high).

Increasing K or t will decrease TAC with little effect on TAD. On the other hand increased frequency of dialysis (without changing K or t), decreases not only TAC but TAD as well. With increased dialysis frequency, there is a fall in TAC and a dramatic fall in TAD for the same total urea clearance (total weekly cleared volume or TWCW). With high efficiency daily hemodialysis TAC and TAD are close to those of healthy kidneys where the urea TAD is less than 1 mmol/L and TAC is less than 4mmol/L.

The status of daily home hemodialysis

Despite the probability of 10 year survival being 75% in home hemodialysis as compared to center hemodialysis (44%) and peritoneal dialysis (21%)[41], even after adjustment of case-mix and co-morbidity[42], it's use has declined in recent years. For example, the number of US patients on this therapy dropped from 5085 to 2086 between 1980 and 1995 (Health Care Financing Administration 1996). Similar trends have been reported from Europe[43]. An increasing number of elderly and sicker patients starting dialysis may be one of the reasons for this decline in the use of home hemodialysis. Logistical factors and complexity of the procedure itself along with a need for a helper may be some of the other factors impacting this trend.

Home hemodialysis provides the option of short and frequent dialysis with the added convenience of being home based. However time (for the patient) and money (for the provider) have been two major impediments to the concept of shorter more frequent home hemodialysis sessions. More frequent dialysis implies more time spent on machine set up, tear down and disinfection besides escalating cost of dialysis in absence of reusable supplies. Modern machines undergoing final clinical trials will hopefully circumvent these problems by incorporating novel features like built in water treatment systems, use of

positive pressure ultrafiltration and reusable dialysate and extracorporeal circuits[44]. For an average sized person a total weekly Kt/V of 5.0 may be achievable by a daily 2-hour dialysis session. Though the Kt/V needed for adequate dialysis in this setting is not known yet, theoretically it may be postulated that it will be lower than thrice a week hemodialysis because both peak concentrations and TAC are lower at the same Kt/V with more frequent dialysis sessions[45].

Under present circumstances, home hemodialysis is cost effective provided dialysis is continued for at least 14.2 months[46]. As compared with CAPD home hemodialysis provides higher technique survival rates[47] and in patients requiring long term dialysis it turns out more cost effective than CAPD[48]. A combination of higher efficiency and simplified machinery and the high cost of hospital based hemodialysis may permit a resurgence of home hemodialysis in a significant segment of a subgroup of ESRD patients.

SUMMARY AND CONCLUSIONS

A vital conceptual difference between intermittent and continuous dialysis therapies is the difference in the relationship between Kt/V urea and dietary protein intake. For a given level of protein intake the intermittent therapies require a higher Kt/V urea due to the reasons mentioned above. The recently released adequacy guidelines by DOQI for intermittent and continuous therapies are based on these assumptions. The link between adequacy targets and patient survival is well documented for an intermittent therapy like HD. For a continuous therapy like CAPD however, the evidence linking improved peritoneal clearance to better survival is not as direct. However, present consensus allows one to extrapolate results based on HD. The concept of earlier and healthier initiation of dialysis is gaining hold and incremental dialysis forms an integral aspect of the whole concept. Tools like urea kinetic modeling give us valuable insight in making mathematical projections about the timing as well as dosing of dialysis. Daily home hemodialysis is still an underutilized modality despite offering best survival figures. Hopefully, with increasing availability of better and simpler machines its use will increase.

Still several questions remain unanswered. Despite availability of data in hemodialysis patients suggesting that an increased dialysis prescription leads to a better survival, optimal dialysis dose is yet to be defined. Concerns regarding methodology of such studies and conclusions thereof has been raised[49]. Other issues relating to design of the studies, variation in dialysis delivery, use of uncontrolled historical standards and lack of patient randomization etc also need to be considered when designing such trials. Hopefully an ongoing prospective randomized trial, namely the HEMO study[22], looking at two precisely defined and carefully maintained dialysis prescriptions will provide some insight into adequacy of dialysis dose and survival. In diabetic patients, the relationship between outcome and dialysis dose needs to be better defined. Data relating adequacy of dialysis to outcome in a pediatric population is not available.

In dialysis therapy, the Risk/Dose (R/D) function does not bear a linear relationship[50]. This together with a lack of proof equating peritoneal to renal clearance lends some uncertainty to the validity of the recommendation that there is a linear and constant decrease in RR for std (Kt/V) [*equivalent standardized Kt/V calculated from average predialysis BUN for any frequency and / or combination of intermittent and continuous dialysis ref*[51]] up to 2.3 as reported in the CANUSA study. Due to the complex nature of this problem it may be prudent to undertake a multi- center trial with std (Kt/V) prospectively randomized to either 2.0 or 2.4[51]. This would provide a reliable database to evaluate the R/D function over this critical range of normalized peritoneal urea clearance. Likewise in PD, the postulated linearity between dialysis dose and outcome needs to be studied in a prospective randomized manner. The amount of dialysis dose required for malnourished patients, diabetic and pediatric patients needs to be better defined. The role of aggressive dialysis in reversing malnutrition needs to be studied and studies need to be done to identify the most scientific use of V in malnourished patients.

Justification of a healthy start / incremental dialysis based on outcome measures needs to be established and it's cost effectiveness validated by clinical trials. Again, a prospective randomized controlled trial comparing incremental dialysis with dietary protein restriction in patients with GFR $\leqslant$ 10.5 ml/min/1.73 m^2 with properly defined outcome measures like morbidity, mortality, decline of GFR and quality of life needs to be conducted. Comparisons of incremental hemodialysis and incremental peritoneal dialysis need to be made especially with regard to technique survival and preservation of residual renal function (RRF).

It is clear that much still needs to be done as far as achieving adequacy in intermittent and continuous modes of dialysis therapies is concerned. Hopefully in the next few years we will have answers to at least some of these questions.

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