Measurement of Hemodialysis Adequacy in a Changing World

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Defining adequacy of dialysis remains an elusive goal. The application of the Kt/V_{urea} concept to clinical dialysis was a major improvement in trying to define a dialysis dose. Intuitively, the Kt/V concept makes a great deal of sense: the urea clearance of the dialyzer during dialysis (K), multiplied by the time (t) of dialysis, divided by the patient's urea distribution volume (V) ought to give the best number to compare the efficiency of dialyses that patients receive. There are, however, many pitfalls associated with the whole Kt/V_{urea} concept.

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Key words

Adequacy, Kt/V, direct dialysis quantification, length of hemodialysis

Introduction

Kt/V in itself does not define "adequacy"; it only establishes that a certain quantity of dialysis was delivered, and even that uncertainly. It assumes that urea generation, retention, and elimination reflect those of other toxins and that the most important toxins are those of small molecular weight. It does so through a mathematical trick that assumes that using concentration changes of urea establishes the mass removed. To do so, several assumptions are made about urea production, removal by other routes, and distribution in body compartments during dialysis. It also assumes that all these factors are the same in all patients. This final assumption throws doubt on the whole concept. The many Kt/V_{urea} formulas with markedly different outcomes point out that even minimally different physiological assumptions made by different investigators have major effects on the resulting Kt/V_{urea} number [1]. Movilli has pointed out that there are now well over a dozen equations with different assumptions of the influence of ultrafiltration, urea generation rate, and disequilibrium that lead to a variation as great as 50% [1]. Furthermore, Kt/V_{urea} assumes that the required dose of dialysis is proportional to the total body water.

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Problems using Kt/V_{urea} with various dialysis methods

Kt/V is difficult to use for continuous dialysis methods, since it requires a separate measurement of K and calculation of V. Furthermore, V must be calculated from formulas developed in subjects without renal failure [2,3]. Finally, V calculated with these two formulas does not give the same result in the same patient.

As the frequency of dialysis increases, Kt/V_{urea} cannot be compared by simply adding individual dialysis results for a weekly total. It cannot be compared or added to remaining renal function without several new assumptions and complicated mathematical formulas [4,5]. The mathematical sophistication and convoluted terminology have reached bizarre levels and have inclined many to use a simple urea reduction ratio or to ignore Kt/V_{urea} totally, relying only on predialysis blood urea nitrogen concentration and time of dialysis. The use of poorly defined and differently measured Kt/V_{urea} to compare widely divergent patient populations in different countries makes the confusion worse. Things are not getting easier, as the frequency of dialysis reenters as a major contributor to dialysis adequacy and patient well-being; the more often the patients are dialyzed, the better off they are, even if Kt/V_{urea} is lowered or held constant [6–9].

Problems with using Kt/V_{urea} for adequacy

In some careful studies, where sophisticated statistical techniques have been used to ensure that other factors that may influence outcome remain constant, even fairly large variations in Kt/V_{urea} have had no influence on outcome [10,11]. There has never been unanimity on how to measure Kt/V, how long to wait for urea equilibration, and what factors to put in for urea generation, disequilibrium, or extrarenal removal. The assumption that all patients behave similarly in all these respects is physiological simple-mindedness.

It is also hard to accept the DOQI (Dialysis Outcomes Quality Initiative) guidelines that a Kt/V_{urea} of 1.3 (single pool model) or 1.2 (double pool) if used three times per week is adequate [12]. Both Charra in France [13] and results from the Japanese dialysis registry [14], including over 100 000 patients, show improvement in survival with increasing Kt/V_{urea}, that goes beyond a Kt/V_{urea} of 1.6 used three times per week. Still, for all its problems, Kt/V remains a parameter that is much superior to predialysis blood urea nitrogen (BUN). It is clear that concentration measurement of predialysis urea is not enough. The most lethal combination in dialysis is

underdialysis and protein malnutrition, yet patients with these characteristics have the same predialysis BUN as well-dialyzed patients with a high protein intake.

Adequacy and length of dialysis

In a given patient V is essentially stable and Kt/V may be increased by increasing K or t or both. Kt may be increased with shorter time, if the increase in K overcompensates for the drop in t. An assumption that the outcome in dialysis patients depends only on Kt/V inclined nephrologists to increase efficiency of dialysis and shorten dialysis time. Such an approach neglected the importance of removal of "middle molecules" and other substances like phosphorus, which have poor transcellular diffusibility. Even more importantly, short dialysis time precludes achievement of true dry body weight and control of blood pressure [15]. Good control of blood pressure decreases cardiovascular morbidity, which is by far the leading cause of death in dialysis patients [15].

Adequacy and dialysis frequency

The escalating interest in increasing dialysis frequency now brings even more complexity to the definition of optimal or adequate dialysis. The results of many clinical studies with a cumulative total of over 200 patients clearly show that increasing dialysis frequency is more important than increasing time and Kt/V_{urea} of dialysis for patient well-being [6–9,16]. However, how to express the beneficial effects of increased frequency remains unknown. In the mid-1970s the eradication of clinical symptoms of uremia, acceptable hematocrit without the need of blood transfusions, well-controlled blood pressure without blood pressure medications, normal nerve conduction velocity, and good nutrition, as judged by serum albumin, were considered as indicating adequate therapy [17,18]. Another approach at that time was the design of an index combining blood pressure values, weight gains, urea and creatinine variations, and potassium changes [19]. Lopot and Valek have more recently suggested the use of time-averaged deviation of urea, as a measure of the unphysiology of intermittent hemodialysis [20]. A third attempt, to mathematically increase Kt/V_{urea} as frequency increases, the standardized Kt/V_{urea} (std Kt/V_{urea}) [4], seems totally inadequate since it is not based on clinical correlations and will only add more confusion to an already confused terminology.

Three decades ago, it was clear that increasing the frequency of dialysis was much more important than increasing the dose [6–8]. The improvement that followed the increased frequency by far exceeded what one can expect by applying the std Kt/V_{urea} concept to these data [6–8]. There are many other factors that need to be considered, measured, and mathematically expressed to create an index of the unphysiology of intermittent hemodialysis. This necessarily needs to capture both differences in speed and frequency of hemodialysis. The proposed index must be checked to correlate with clinical outcomes. Candidates contributing to such an index may include deviations from normal of bicarbonate and potassium, which, unlike BUN, are toxic at both high and low values. Osmolality changes per hour and over a whole dialysis session, weight oscillations, and ultrafiltration rates are other candidates to consider. How to quantify such an index and use it together with Kt/V_{urea} will prove difficult, but will allow stimulating discussions in the future.

Direct measurement of dialysis dose

Direct dialysis quantification methods are quite appealing. Much of the problem with Kt/V rests on endless discussions and disagreement of equilibration times, urea generation, and extrarenal urea removal. In reality, there is probably no equilibration time applicable to all patients. Some individuals transfer urea very quickly and need no equilibration time; others equilibrate very slowly and may need hours [21]. Perhaps this is one of the explanations for the difficulty in relating Kt/V to clinical outcome parameters [10,11]. Much of the guesswork that bedevils the use of concentration as a surrogate for mass can be avoided by using direct measurements of the mass of urea removed, rather than trying to infer it from changes in urea concentration. Computerized on-line urea monitors do so by measuring the urea concentration in the spent dialysate, as it flows past the probe, and integrating the area under the curve; however, this is very expensive and its accuracy doubtful [22,23]. Much better is the ingenious collection method of Ing *et al.* [24], who simply insert a small T-tube into the dialysate outflow line and let a fraction of dialysate slowly drip into a container throughout the whole treatment. At the end of dialysis the sample in the container has the same concentration as a total dialysate collection. It allows very accurate measurements of urea. Second, since the drop rate from the T-tube is directly dependent on the dialysate flow rate, variations in the latter are compensated [24]. This method shows that a simple device, available for pennies, beats a much more complicated setup for which one would have to pay thousands of dollars.

Indices for optimal dialysis in the future

The time is coming to depart from the concept of dialysis adequacy and develop indices of optimal dialysis. It is clear that Kt/V as the sole index of dialysis adequacy is becoming obsolete. The future index certainly will include some kind of small molecule removal measure, probably by direct quantification of dialysis dose, but also control of solutes such as serum bicarbonate, potassium, and phosphate within physiological ranges. Finally, an excellent control of extracellular volume and, thereby, blood pressure must be included in any measure of optimal dialysis. Time and frequency of dialysis will have to be adjusted to achieve these goals. Short, thrice-weekly hemodialysis, in patients without residual renal function, may be completely abandoned in the future. The final measure of optimal dialysis will be the probability of survival in hemodialysis patients similar to that in populations without renal failure adjusted for age and comorbid conditions.

Much new is coming again in dialysis. We live in interesting times. This is an old Chinese curse, but it beats dying of boredom at dialysis meetings!

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