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Reduction in mortality is a general goal of medicine. For those caring for patients with end-stage renal disease a particular urgency to address this issue exists in the United States due to unfavorable outcome data by international comparisons.

The Problem According to International Comparisons

An international study of 5-year mortality among ESRD patients showed higher mortality rates for patients treated in the United States compared to those treated in Japan or in countries of the European Dialysis and Transplant (EDTA) Registry (1). (Data from dialysis and transplant patients were combined because of large differences in transplantation rates between countries.) This study dealt with the relatively higher ages and greater proportion of diabetic ESRD patients in the United States by studying separately specific age categories for diabetic and non-diabetic patients. The higher mortality was consistent for all U.S. patient groups, with the exception of pediatric and very young adult groups. A recent study by Held et al. (unpublished data) showed similar alarming findings when adult U.S. ESRD patient groups were compared to those treated in Canada.

These international comparisons of ESRD patient mortality may be subject to potential biases. For example, the U.S. mortality experience excludes the relatively high mortality of the first 3 months of ESRD by starting analysis on day 90 of ESRD. U.S. patients may also have a higher degree of comorbidity and/or more complete reporting of death. On the other hand, compared to Japan and the sum of EDTA countries, transplantation rates in the United States are relatively high, thus benefiting ESRD results in the United States. Also, for the comparison with Europe, one may argue that U.S. results should be limited to white patients ("European Americans"); however, their mortality is greater than that of blacks overall, except in younger age groups (2). The magnitude of the observed differences and the described biases as well as confirmation with three different registries of Canada, Europe, and Japan make it likely that mortality is higher in the United States.

Potential Causes for High Mortality in Hemodialysis Patients

Among hemodialysis patients, there may be two major reasons for the relatively high mortality in the United States: medical care and dose of therapy. General medical care issues may play a role, and an enhanced focus on chronic dialysis therapy during the training of nephrologists would be desirable. The dose of hemodialysis therapy has been an issue surrounded by controversy, yet recent evidence argues that it may substantially contribute to the mortality among dialysis patients.

Dose of Hemodialysis

The dose of hemodialysis therapy has been quantified in many ways, as recently reviewed by Hakim et al. (3). The concept of toxin removal (clearance (K) × treatment time (t) adjusted for patient size or the toxin's distribution volume (V) is logical, although somewhat simplistic. Some of the controversy centers around which molecule should be the marker substance for the proper prescription of dialysis dose. Vanholder and Ringoir (4) summarize the multitude of possible candidates by listing one page of uremic toxins with potential toxicity. Although urea by itself is not very toxic, it is a marker for products from protein catabolism, and a majority of "uremic toxins" are derived from proteins. Lacking other widely available indicators of protein catabolism we are left at present with urea, despite known limitations due to its low molecular weight,

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large distribution volume, and dependence on liver function.

Thus, when we approach the issue of dialysis dose from a practical rather than a research point of view, measuring the volume of blood cleared of urea per urea distribution space becomes the only feasible way of monitoring hemodialysis therapy for over 100,000 patients in the United States. Several potential problems need to be considered when assessing the dose of dialysis from Kt/V of urea or urea reduction ratio (URR) (3).

Delivered Dialysis Dose Predicts Outcome

The concept that a lower dose of dialysis is associated with poorer patient outcomes is empirical, particularly for patients who have lost their residual renal function. Dialysis therapy is designed to replace in part the function of the failed kidneys and needs to meet a certain minimum replacement or "dose," i.e., more replacement is likely to be better for patients than less. Given that dialysis replaces less than 10% of the normal creatinine clearance per week, a correlation of lower dose with worse uremia and worse outcome would be expected.

Evidence for such a correlation comes from the neurophysiological studies of Teschan (5) and from the National Cooperative Dialysis Study (6). These studies focused on morbidity outcomes and arrived at the same concept of a weekly dose of dialysis described by Kt/V, with the protein catabolic rate as a modifier.

The U.S. Renal Data System (USRDS) sheds new light on this decade-old topic. In a study including a random sample of nearly 4000 U.S. hemodialysis patients, Held et al. (7) assessed the dose of hemodialysis. The prescribed Kt/V averaged 1.0, and 25% of patients had a level of less than 0.8. No correlation between prescribed Kt/V and mortality risk could be established. However, the same investigators found the average dose of dialysis delivered to be markedly lower than that prescribed for patients in whom delivered therapy could be measured from pre- and postdialysis blood urea nitrogen (BUN) ($n = 381$). Delivered Kt/V as calculated from the URR did show a statistically significant correlation with the mortality risk, i.e., patients whose Kt/V was 0.1 higher had a relative risk of dying that was 8% lower ($RR = 0.92$, $p < 0.05$). This study of patients starting therapy in 1986–87 is currently being expanded with a USRDS study of 4000–5000 hemodialysis patients to substantiate these findings and provide further insights on therapy and outcomes in 1991–92. Additionally, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, is beginning to fund a new multicenter dialysis study to address morbidity and mortality as they relate to dialysis therapy variables.

What Can Be Done Now?

Until new study results are available it appears that action is required to improve outcomes among hemodialysis patients. Given the low average dose prescribed in the United States and available, although somewhat incomplete, evidence, it appears to be imperative to raise the average dose of hemodialysis in the United States. This increase should be in the delivered, not just the calculated dose of dialysis, with a special focus on those patients for whom delivered Kt/V is particularly low. To accomplish this goal in practice, dialysis time needs to be prolonged and/or dialysis efficiency needs to be increased.

Increase the Dialysis Time

The duration of hemodialysis in hours per week is much lower in the United States than in Europe (8) or Japan. A strong correlation was found between shorter duration of non-high-flux dialysis with higher mortality risk in the United States (9) and likely reflects the fact that duration (t) is a major determinant of Kt/V. Additionally, short dialysis may make it more difficult to achieve the patient's dry weight and may lead to increased mortality. Patients prefer shorter dialysis treatments and may not feel the adverse effects of an insufficient dose of dialysis for a prolonged period of time. With short treatment times, dialysis dose is more markedly affected when patients reduce their treatment time against medical advice and when the dialysis clock starts running before the blood flow reaches desired levels.

Thus, additional efforts need to be directed at increased patient and staff education regarding the benefits of a larger dose of dialysis. The full treatment needs to be delivered consistently by the minute and the duration of dialysis increased whenever possible in order to raise the average dose of dialysis. For patients with delivered Kt/V below or near 1.0 an additional 30–60 minutes per treatment would be desirable but may be costly in some settings. In those situations attention to detail and improved efficiency may offer less costly alternatives.

Increase the Dialysis Efficiency

Increased efficiency can be achieved at essentially no cost through maximizing blood flow rates beyond 300 ml/min and avoiding a very slow increase in blood flows over the first 30–60 minutes. The use of larger, more efficient dialyzers would also increase clearances. For units reusing dialyzers, the additional cost of larger dialyzers is minimal when considered per dialysis treatment. Monitoring of the delivered dose of dialysis is important, since an increase in dialyzer surface area from 1.0 to 1.2 m^2 increases urea clearance (K) by a much smaller proportion.

Avoid a False Security in Measured Kt/V

Prescribing Kt/V according to manufacturer's specifications of K may serve as a guideline, but it is critical to monitor the lower dose of dialysis actually delivered to the patient. Even monitoring Kt/V of

urea from kinetic modeling or from URR may provide misleading results. Several formulas overestimate Kt/V from URR, as described by Daugirdas (10). Compliant patients who require little ultrafiltration may have a lower calculated Kt/V than those requiring large ultrafiltration volumes. Samples for BUN must be obtained while the blood pump is turned off after flushing the blood lines, since even small amounts of recirculation would otherwise yield false low postdialysis BUNs and an overestimation of URR and Kt/V. Relatively short, highly efficient hemodialysis leads to a deceptively low postdialysis BUN followed by a greater rebound than with standard dialysis and may therefore require a Kt/V of approximately 0.2 more than with "slower" dialysis.

Several other perhaps obvious points should not be overlooked. Patients who miss dialysis treatments may have an excellent Kt/V while treated yet be underdialyzed overall. Similarly, patients may get their full treatments on days when pre- and postdialysis BUN is measured but shorten their treatments on other days. Residual renal function may contribute substantially to the total clearance, particularly in the first year of therapy; however, gradual loss of this function over time is common and must be recognized in order to avoid subsequent underdialysis.

Renal Transplantation

Patient survival is markedly improved in transplant recipients compared to an appropriately controlled dialysis population (11). Thus, enhanced availability of organs would allow a greater fraction of patients to be transplanted for improved patient survival.

Unresolved Issues

Several studies suggest that nutrition deserves additional attention (12). While a reduced serum albumin level has been significantly correlated with high mortality (8), it is not certain at present whether raising the albumin level will result in improved outcomes. A low serum albumin level may be the result of uremic anorexia among patients who initiate dialysis therapy late or whose dialysis dosage is inadequate. Future studies need to establish the role of earlier initiation of dialysis, higher dose of dialysis, or nutritional supplementation in improving nutritional status and patient survival. In the meantime a greater focus on maintaining adequate nutrition will likely benefit dialysis patients.

Conclusion

The correlation of low delivered dose of dialysis with elevated risk of morbidity and mortality indicates that more dialysis is better than less. Rather than providing a minimal or barely "adequate" dose of dialysis, it would be advantageous to seek a desirable dose beyond which little additional benefit may be achieved. By international standards, U.S. patients receive a remarkably low dose of hemodialysis (8) and have high mortality rates (1). Given this, an improvement in mortality among dialysis patients is likely to be achievable by increasing the delivered dose of hemodialysis.

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On its face, the question of how to reduce dialysis patient mortality is straightforward and clinical in nature: What changes in caregiver and/or patient behaviors will result in better patient survival? Our system of dialysis care is, however, embedded in a complex attitudinal, institutional, and public policy structure, and an effective attack on the problem of patient mortality rates must deal with all of these structural dimensions.

The literature on quality assurance teaches us to

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