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Is Early Initiation of Dialysis Harmful?

Matthew B. Rivara, MD and Rajnish Mehrotra, MD, MS

Kidney Research Institute and Harborview Medical Center, University of Washington, Seattle, WA

Matthew B. Rivara: mbr@uw.edu; Rajnish Mehrotra: rmehrotr@uw.edu

Abstract

Over the past two decades in the United States, there has been an inexorable increase in the mean estimated glomerular filtration rate (eGFR) at which patients are starting maintenance dialysis. Data from observational studies using eGFR derived from serum creatinine-based estimating equations has suggested that initiating dialysis at higher levels of kidney function may be associated with increased incidence of adverse clinical outcomes including mortality. At the same time, observational studies using time urinary clearances to measure eGFR have not demonstrated the same relationship, and instead of shown either no association between eGFR at dialysis initiation and subsequent outcomes, or increased survival with higher native renal clearances. There are numerous potential harms from the dialysis procedure itself, including adverse effects on cardiac structure and function, hemodynamic disturbances, increased oxidative stress, and risk for infection due to the presence of foreign objects such as dialysis catheters. Notwithstanding these potential harms, the IDEAL trial, the only controlled clinical trial published to date examining this question, showed no effect of eGFR on any of the examined clinically relevant outcomes at the start of maintenance dialysis. Thus, the available data do not support the use of renal function as the primary guide for determining timing of initiation of chronic renal replacement therapy. The nephrology community should transition to examining other potential approaches to addressing this important question. One potential area of interest is uremic symptomatology and health-related quality of life, though currently available data are indeterminate regarding which symptoms improve with the start of dialysis. Further research is needed to identify patient-centered approaches for decision making around dialysis initiation that will optimally improve survival and other important outcomes.

OVERVIEW

In the US, more than 110,000 individuals with end-stage renal disease (ESRD) initiate renal replacement therapy each year; most have not undergone adequate medical or psychosocial preparation for the initiation of maintenance dialysis, in part because of limitations in our understanding of the optimal timing for initiation of maintenance dialysis (1). In the 1990s, clinical practice guidelines emphasized the primacy of estimated glomerular filtration rate (eGFR) in deciding when to start renal replacement therapies and over the last two decades there has been a continual increase in the mean eGFR at the time of initiation of renal replacement therapy (1). Yet, it remains uncertain if starting maintenance dialysis at a higher

eGFR has resulted in any meaningful improvement in patient outcomes. Additionally, over the past decade, numerous observational studies using serum creatinine-based estimates of renal function have shown a higher risk of death with a higher eGFR at the time of dialysis initiation (2). Some investigators have raised the question of whether an “early start” approach to initiation of maintenance dialysis may be harmful, and instead have advocated delaying the start of renal replacement therapy until the appearance of a disabling burden of symptoms attributable to the uremic state (3). In this article, we present a discussion of available data in an attempt to address the important question of whether initiation of dialysis at higher eGFR is harmful.

eGFR AT INITIATION OF DIALYSIS AND MORTALITY – OBSERVATIONAL STUDIES

Over the past decade, at least 10 studies have examined the association between level of estimated kidney function (using serum creatinine-based estimating equations) at initiation of dialysis and subsequent clinical outcomes including mortality (2). These studies have consistently demonstrated a higher mortality risk with higher eGFR, with a recent meta-analysis reporting a pooled adjusted hazard ratio for all-cause mortality of 1.04 (95% CI, 1.03–1.05) per 1 ml/min higher GFR at dialysis initiation (4). Each of these studies has also shown that patients who initiate dialysis at higher levels of kidney function are generally sicker with higher prevalence of diabetes, cardiovascular disease, and other comorbidities. This observation raises the possibility of confounding by indication and residual confounding such that patients who start dialysis at higher eGFR have co-existing conditions that make them poorly tolerant of symptoms of advanced chronic kidney disease (CKD) and higher risk of death due to their underlying comorbidities.

In contrast to observational studies using serum-creatinine based estimating equations, studies that have used timed urinary clearances to measure GFR have shown either no association between kidney function at the time of initiation of dialysis and subsequent outcomes, or a lower mortality risk in patients with greater native renal clearances (2). This raises a concern for misclassification bias, that in patients with significantly reduced kidney function, serum creatinine provides a measure of muscle mass in addition to reflecting the GFR; thus in patients with advanced kidney disease, a higher eGFR using serum creatinine-based estimating equations reflects muscle wasting (sarcopenia) and protein-energy-wasting (2,5). Hence, in observational studies using eGFR, sarcopenia – an independent predictor of mortality – confounds the relationship of kidney function at initiation of dialysis with subsequent mortality and the results of such studies may not reflect the harmful effects of the dialysis procedure itself.

POTENTIAL MECHANISMS OF HARM FROM THE DIALYSIS PROCEDURE

The aforementioned observational studies continue to leave a lingering concern that initiation of maintenance dialysis at a higher eGFR carries an increased risk for adverse clinical outcomes, in part from the dialysis procedure itself. Table 1 lists some potential mechanisms for harm from the dialysis procedure. Recent studies have shown that the HD procedure results in regional wall motion abnormalities, which has been associated with

higher one-year mortality (6). Significant fluctuations in overall levels and flux of potassium, magnesium, and calcium occur in patients undergoing both HD and PD, and these have been associated with cardiac dysrhythmia, worsening of congestive heart failure, and sudden cardiac death (7,8). HD is characterized by frequent wide fluctuations in blood pressure, including episodic hypotension, which has been associated with watershed brain infarcts as well cardiovascular morbidity and mortality (9). Elevated biomarkers of oxidative stress are widely prevalent in patients with ESRD, have been shown to increase after initiation of maintenance dialysis, and have been linked with adverse clinical outcomes in this population (10). Though the advent of erythropoiesis-stimulating agents (ESAs) has dramatically reduced the requirement for regular red blood cell transfusion in the ESRD population, several studies have identified significant safety concerns with ESA use, including increased risk for stroke (11). Both PD and HD patients are also at increased risk of infection due to the presence of foreign objects such as central venous catheters and peritoneal dialysis catheters. And finally, the exposure of the blood compartment in HD patients to the dialysis equipment including tubing and the dialysis filter have been associated with adverse clinical outcomes (12). Further research is needed to elucidate if any of these potential harms of the dialysis procedure underlie the association between higher eGFR at dialysis initiation with risk for death.

eGFR AT INITIATION OF DIALYSIS AND MORTALITY – EXPERIMENTAL STUDY

To date, the IDEAL study, published in 2010, is the only clinical trial that has examined the association of kidney function at dialysis initiation with patient outcomes (13). In this trial, 828 patients in 32 centers in Australia and New Zealand were randomized to begin renal replacement therapy at eGFR of 10–14 ml/minute/1.73 m² (the “early” group) or at eGFR of 5–7 ml/minutes/1.73 m² (the “late” group). The major finding from the study was that there was no significant difference between the groups in survival or any other clinically important outcome, including hospitalizations or quality of life. The result of this study has to be interpreted in light of the fact that nearly 20% of the “early” group initiated dialysis at an eGFR above 7 ml/min/1.73 m² and over three quarters of patients in the “late” group had an eGFR below 10 ml/min/1.73 m². Additionally, study subjects had less comorbidity and had been under the care of a nephrologist for a longer period of time than the vast majority of ESRD patients in the United States, raising concerns about external validity. Notwithstanding these limitations, the IDEAL study stands as the definitive clinical trial in this area, and importantly did not show an adverse impact of initiating dialysis at a higher eGFR.

SHOULD SYMPTOM BURDEN GUIDE DECISION TO INITIATE DIALYSIS TO MITIGATE RISK?

Even though the indications that prompt the initiation of dialysis in clinical practice today are not known, alleviation of uremic symptoms is often considered as one such indication. However, several cross-sectional studies using a variety of instruments have shown an equally high prevalence of physical, emotional, and psychological symptoms in patients

with advanced CKD as in those with ESRD undergoing dialysis (14,15). Initiation of dialysis is associated with increase in dietary intake and improvement in measures of protein-energy wasting (16,17). Yet, remarkably little is known which other uremic symptoms consistently improve upon initiation of dialysis since no published study has prospectively investigated how the burden of symptoms in patients with CKD changes with initiation of renal replacement therapy. A recent study of 3702 nursing home residents showed a decline in overall functional status with the start of renal replacement therapy, a finding that remained significant even upon adjustment for accelerated functional decline in the 3 month period immediately preceding dialysis initiation (18). Hence, it remains unclear whether the clinical paradigm of initiating dialysis solely to relieve uremic symptoms is feasible or effective in improving patient-centered outcomes.

CONCLUSIONS

The data presented in this article challenge the paradigm of using renal function as the primary guide for initiation of maintenance dialysis. Notwithstanding the observational data linking higher eGFR at dialysis initiation with higher mortality, the IDEAL trial showed no significant difference in outcomes based upon level of renal function at the time of first maintenance dialysis treatment. The impact of the timing of dialysis initiation on patient symptoms and quality of life, as well as on costs to the health care system, is also unclear. It is unlikely that a controlled study similar in scope and size to the IDEAL trial will be repeated in the near future. Given this, rather than continue to question at what level of measured or estimated kidney function maintenance dialysis should be initiated in patients with advanced CKD, the nephrology community should transition to developing an evidence-based patient-centered strategy for initiation of maintenance dialysis. Instead of focusing on eGFR, there is thus a need to generate the evidence necessary to develop a strategy that will allow dialysis therapy to reduce symptom burden and improve health-related quality of life.

Additionally, it is also important to remember that delayed initiation of maintenance dialysis does not mean delayed preparation for dialysis (19). Less than 25% of individuals starting dialysis in the United States each year have had predialysis care from a nephrologist for greater than one year (1). Eighty percent of U.S. ESRD patients begin dialysis with a central venous catheter, and by the fourth month of treatment, less than half of all patients received dialysis through an arteriovenous fistula or graft (1). These represent significant areas for improvement with clear benefit for patients, regardless of the timing of renal replacement therapy itself. As nephrology enters an era of focus on patient-centered outcomes, there remains a compelling need for further research to assist clinicians and their patients to optimally time dialysis initiation.

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Table 1

Potential mechanisms of harm from the hemodialysis or peritoneal dialysis procedure

	Modality	Mechanism
1	HD	Recurrent episodes of myocardial ischemia and stunning leading
2	HD	Hemodynamic fluctuations related to ultrafiltration volume
3	HD	Ischemic brain injury related to intradialytic hypotension
4	HD	Chronic metabolic alkalosis through exposure to high bicarbonate dialysate
5	HD	Exposure of the blood compartment to dialysis equipment, tubing, and water
6	HD	Microemboli due to microthrombi in the dialysis filter
7	PD	Systemic or local exposure to high glucose concentrations
8	HD or PD	Abnormalities and fluctuations in levels of potassium, magnesium, and calcium leading to risk for cardiac arrhythmia, heart failure, and sudden cardiac death
9	HD or PD	Removal of dialyzable vitamins and minerals
10	HD or PD	Increased prevalence of oxidative stress contributing to cardiovascular morbidity and mortality
11	HD or PD	Exposure to erythropoiesis-stimulating agents
12	HD or PD	Loss of endogenous renal function
13	HD or PD	Infections – catheter related blood stream infections (HD) or peritonitis (PD)

eGFR, estimated glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis