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Repercussions of early versus late initiation of dialysis

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ABSTRACT

Despite the widespread use of chronic dialysis, there remains a lack of consensus about the optimal time for initiation of renal replacement therapy. Recommendations from the National Kidney Foundation Kidney Disease Outcome Quality Initiative are generally used as the guideline. This has resulted in a trend in the past decade toward earlier initiation of dialysis, especially in the elderly. The associated burden of comorbidities in the elderly population has resulted in greatly reduced survival outcomes. Here, the data obtained from retrospective cohort studies have been corroborated with a recent randomized control trial conducted in Australia and New Zealand (IDEAL study). There are limitations to consider from the IDEAL study that originate from different confounding factors that intervene in the test population. The present paper is an evidence-based review of the literature, focusing on diminution of survival outcomes following the early initiation of dialysis.

Keywords: Hemodialysis. Glomerular filtration rate. Mortality. Malnutrition. Peritoneal dialysis.

Repercusiones del inicio temprano y del inicio tardío de la diálisis

RESUMEN

A pesar de que el uso de la diálisis crónica está muy extendido, aún no existe consenso en cuanto a cuál es el mejor momento para comenzar el tratamiento renal sustitutivo, por lo que se suelen utilizar como referencia las recomendaciones de la Iniciativa para la Calidad de los Resultados de la Insuficiencia Renal de la Fundación Nacional del Riñón (NKF-KDOQI). Esto ha provocado que durante la última década hay surgido una tendencia a iniciar la diálisis antes, especialmente en el caso de las personas de edad avanzada, lo que ha conllevado a una reducción considerable de las tasas de supervivencia, debido a la mayor carga de comorbilidades que sufre esta población. Los datos de estudios de cohorte retrospectivos han sido corroborados por el ensayo controlado aleatorizado que se ha realizado recientemente en Australia y Nueva Zelanda, el estudio IDEAL. Este estudio tiene ciertas limitaciones, ya que existen diferentes factores de confusión que afectan a la población estudiada. Nuestro trabajo es una revisión basada en la evidencia que se centra en la reducción de las tasas de supervivencia que se ha producido con el inicio temprano de la diálisis.

Palabras clave: *Hemodiálisis. Filtrado glomerular. Mortalidad. Malnutrición. Diálisis peritoneal.*

INTRODUCTION

Hemodialysis therapy assists patients in the management of uremia and volume control through diffusion and convection. This approach purports to lead to decreased morbidity and mortality, as well as to improve the quality of life. In order to improve survival, the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-DOQUI) recommended that dialysis be initiated when weekly renal KT/V_{urea} decreased to less than 2.0. This approximated an estimated glomerular filtration rate (e GFR) of 10.5 ml/min/1.73 m^2, unless 3 of the following criteria were fulfilled: *1)* stable or increased edema-free body weight; *2)* no evidence of malnutrition (normalized protein equivalent of total nitrogen appearance >0.8), and *3)* absence of clinical symptoms and signs due to uremia[1]. *This was based on NKF-DOQUI peritoneal dialysis guidelines because of the lack of outcome studies evaluating residual renal function in hemodialysis*. Recommendations that were updated in 2006 with initiation of dialysis when the eGFR was <15 ml/min/1.73 m^2 as predicated by a previous evaluation of benefits and risks by the nephrologist, and with eGFR >15

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ml/min/1.73 m^2 in symptomatic patients. European guidelines recommended that dialysis should be instituted[2] when the eGFR is <15 ml/min/1.73 m^2. This recommendations were supported by data from the Canada and United States study (CANUSA study) of continuous ambulatory peritoneal dialysis[3]. Later refuted by the ADEquacy of PD in MEXico (ADEMEX) and Hemodialysis (HEMO) studies[4,5].

Data selected from the United States Renal Data System (USRDS) demonstrated an increase in the frequency of patients initiating dialysis (hemo and peritoneal dialysis)[6], with estimated eGFR above 10 ml/min/1.73 m^2. In 2005, 30% of patients started dialysis at eGFR values of 10-14.9 ml/min/1.73 m^2, and 15% at eGFR greater than 15 ml/min/1.73 m^2 (compared to 15% and 4% respectively, in 1996). The frequency of eGFR ≥10 mlL/min/1.73 m^2 increased to 54% from 25% in 1996, especially in patients over the age of 75 years at the time of initiation of dialysis[6]. The individuals who recommended the increased frequency of early initiation relied heavily on eGFR equations, financial reasons, and comorbidities (end-stage renal disease (ESRD) due to diabetes (43% in 1996 and 44.2% in 2005). This approach burdened the Medicare-ESRD program with 18,076 more patients (started in 2005), at an approximate additional annual cost of $641 million in 2006[7].

Therefore, the goal of this review is to evaluate current literature which describes observational and retrospective studies that were conducted to compare early or late initiation of dialysis, and the influence of these practices in survival in the ESRD population.

EARLY OR LATE INITIATION OF DIALYSIS (table 1)

The suggestion that early initiation of dialysis was beneficial was first given support by Bonomini, et al.[8], showing a 12 year survival of 77% in 82 patients who started dialysis early (mean creatinine clearance CrCl of 12.9 ml/min). These results were compared with 51% in 308 patients who started late (CrCl of 2.1 to 4.8 ml/min). However, the study did not adjust for age or other comorbidities.

A study published by Fink, et al.[9] with patients who initiated dialysis between April 1995 and December 1996, analyzed data obtained from the Health Care Financing Administration (HCFA) Form 2728. Creatinine levels correlated inversely

Tabla 1. Survival outcomes in early versus late initiation of dialysis

Autor year	Study design	No. Patients typr	Dialysis ml/min	eGFR	Renal function at initiation/mortality	Limitations
Fink et al 1999	Retrospective Observational cohort HCFA	5,398	HD/PD	Serum Creatinine	↓Creatinine ↓survival each Scr 1 mg/dl ↑ / 4% ↓ risk of death RR=0.96;P=0,01	HCFA 2728 Inaccurate reporting confounders
Korevaar et al 2001	Prospective	253	HD/PD	E-7.1(2.4) L-4.9(1.7)	↑ mortality late start Adjusted HR 1.66(95% cCl)	Lead-time bias Retrospective Small # patients
Traynor et al 2002	Prospective Glasgow Registry	235	HD/PD	E-10.4 (eCrCl) L- 6.7 Median 8.3	Every ↑ 1 ml/min CrCl 10% ↑ HR P=0.02 Lower eCrCl survive longer	Selection bias Lack of data in initiation Lead time bias
Beddhu et al 2003	Prospective Registry USRDS DMMS II study	2,920	HD/PD	E-5.6 L-10.9	each ↑ 5 ml/min GFR/MDRD ↑ HR 1.14,P=0.002 entire cohort ↑ GFR subgroup; ↑ HR 1.27 for each 5 ml/min ↑ GFR, P< 0.001	Unmeasured confoumders Lead-time/survival bias Lack of data in initiation
Kazmi et al 2005	Retrospective CMS	302,287	HD	< 5 5-7,5 7.6-10 > 10	GFR > 10 42% ↑ risk death	Unmeasured GFR Incomplete comorbidity data Lead time/survival bias
Wright et al 2010	Retrospective USRDS	212,741 (896,546 Incident)	HD/PD	<5 > 5-10 >10-15 >15	GFR< 5 ml/min ↓,HR 0.88 GFR >10-15 ↑ RR,HR 1.15 GFR>15 HR 1.44,P=0.001	Selection bias Retrospective-no causation Lead-time bias Residual confounding
Rosansky et al 2010	Retrospective CMS	81,176	HD	<5, 5-9.9 10-14.9, >15	Unadjusted 1, year mortality 6.8% GFR<5 ,HR 1.27,(5-9.9) 20.1% GFR>15, HR 2.18	No reported comorbidities Unobserved covariates Unmeasured comorbidities
Clark et al 2010	Retrospective Canadian registry	25,910	HD	Mean GFR E-15.5 L-7.1	Mean GFR 7.1 Unadjusted HR 1.48, 95% CI	Observational bias AKI capture patients Lack of data in initiation

GFR: glomerular filtraton rate; E: early; L: late; HD: hemodialysis; PD: peritoneal dialysis; DMMS: dialysis morbidity mortality; CMS: Center for Medicare & Medicaid Services; USRDS: US Renal Data System.

with mortality risk. The relationship sustained after transformation into eGFR, multivariate adjustment for confounders resulted in a relative risk = 0.96; p <0.0001.

In the Netherlands, Korevaar, et al.[10] investigated 253 patients starting dialysis between January 1997 and May 1999 as part of a prospective multicentre study that evaluated mortality at initiation of dialysis in late and early patients. The mean follow-up time was 33-34 months. Thirty-seven percent were late starters with a GFR between 4-9 mL/min/1.73 m^2. There was an increased mortality risk for late starters, although not statistically significant (adjusted HR 1.66, 95% confidence interval (CI 0.95-2.89). The two year survival was 75% (95% CI) in late starters, and 84% in early starters. Traynor corroborated this data, evaluating patients from the Glasgow Royal Infirmary registry. He noticed a 10% increased risk of hazard of death for every 1 ml/min extra creatinine clearance at start of dialysis[11].

Retrospective studies have described an increased risk of death in patients *starting dialysis at higher glomerular filtration rates*.

Beddhu, et al.[12], analyzed patients from the United States Renal Data System (USRDS) Dialysis Morbidity Mortality Wave Study II to determine the associations of modification of diet in renal disease (MDRD) GFR formulation, and also measured CrCl at the initiation of dialysis with subsequent mortality. Higher eGFR at initiation of dialysis was associated with increased risk of death. There were divergent results between MDRD GFR and CrCl calculations attributed to erroneous GFR estimations by the MDRD formula.

In a later study, Kazmi, et al.[13] evaluated data from the Center for Medicare & Medicaid Services between 1996 and 1999, linking three incident dialysis populations and the risk of death based on GFR at initiation of dialysis. After adjusting for all covariates, the increased risk of death in the general population age 18+ years was 42% with GFR >10 mL/min/1.73 m^2 compared with GFR <5 mL/min/1.73 m^2. Patients with ages 67+ years, and a "low risk" subgroup without comorbidities (diabetes, heart failure, atherosclerotic heart disease) had an adjusted increased risk of 25% and 39%, respectively.

The outcomes discussed above correlated with three recently published studies. In the first, Wright, et al.[14], carried out a retrospective analyses of patients entering the USRDS from January 1995 to September 2006. Of the total incident population (896,546), 99,231 patients had an early start (eGFR >15 ml/min/1.73 m^2) and 113,510 had late start (eGFR≤ 5 ml/min/1.73 m^2). Late starters had a 12% reduced risk in mortality (HR, 0.88; 95% CI 0.84 to 0.92; p <0.001*)* whereas there was an 44% increase in mortality risk associated with early starts: eGFR >10 to 15 ml/min/1.73 m^2 (HR, 1.15; 95% CI 1.15 to 1.16; p <0.001) or an eGFR >15 ml/min/1.73 m^2 (HR, 1.44; 95% CI, 1.43 to 1.45; p <0.001).

A second study by Rosansky, et al.[15] investigated an incident ESRD population from 1996 through 2006, using the Center for Medicare and Medicaid Services 2728 form. The goal was to determine if early initiation had survival benefit. Mortality was 20.1% in the early-start and 6.8% in the late-start groups. There was a 3.5-fold greater mortality with an eGFR of 15 ml/min/1.73 m^2 at the initiation of dialysis compared to an eGFR lower than 5 ml/min/1.73 m^2. Male sex, African American race and body mass index (BMI) <25, had a negative effect on survival. High levels of hemoglobin (10.2 g/dl), Asian race, and PCKD or glomerular disease had a positive effect on survival.

A third retrospective study by Clark, et al.[16] in Canada identified 25,910 patients, from the Canadian Organ Replacement Register, between 2001 and 2007. Of those patients, 32.6% initiated dialysis at an eGFR above 10.5 ml/min/1.73 m^2 and 67.4% at an eGFR of 10.5 ml/min/1.73 m^2 or less (mean eGFR 15.5, Standard Deviation [SD] 7.7 ml/min/1.73 m^2 early initiation, 7.1 ml/min/1.73 m^2 , SD 2.0, late initiation). Median follow-up 2.3 years. The early group had higher incidence of coronary artery disease, peripheral vascular and, cerebrovascular disease, diabetes mellitus, and lung disease (early group: 44.9%, 26%, 16.8%, 52.7%, 16.8%; late group: 31.3%, 18%, 13.2%, 43.4%, 12.5%, respectively). The adjusted mortality differential between patients with early and late initiation narrowed after one year of follow-up, but the mortality rates never converged, and the differential began to widen again after two years in the Kaplan-Meier survival curves. After three years, there were 27 more deaths per 1,000 patient-years in the group with early initiation.

The literature presented here compared early retrospective studies that associated patient survival with early initiation of dialysis, in disagreement with later data. The concern was the higher relative mortality rate especially with patients starting at eGFR of 10 ml/min/1.73 m^2 or higher. A possible mechanism might include: recurrent episodes of myocardial ischemia and "stunning myocardium", with fixed systolic dysfunction directly related to ultrafiltration and hypotensive episodes. Since most of the information was retrospective in nature, it is subject to limitations in interpretation of the different covariants that are important in these studies. In order to obtain a clearer picture it would be necessary to carry out randomized control trials.

THE "IDEAL" STUDY

The Initiating Dialysis Early and Late study (IDEAL)[17] was designed as a randomized controlled trial to determine whether initiating dialysis early in individuals with stage V chronic kidney disease reduced the rate of death from any cause. Secondary aims were to determine whether early initiation of dialysis was associated with reduction in cardiovascular and infectious events, and in

complications of dialysis. Between July 2000 and November 2008, 828 patients were recruited at 32 centers in Australia and New Zealand. From these individuals, 404 patients were randomly assigned to an early-start group (eGFR 10 to 14 ml/min) and 424 were assigned to a late-start group (eGFR 5 to 7 ml/min). The eGFR was determined using the Cockcroft-Gault equation, after correction for body-surface area[18]. The MDRD equation was used for comparison. Median duration of follow-up averaged 3.5 years, and both groups did not differ significantly with respect to pharmacologic intervention. At the time of initiation of dialysis, the mean eGFR was 12 ml/min in the early start group and 9.8 ml/min in the late-start group (mean difference, 2.2 ml/min; 95% CI, 1.8 to 2.6; p <0.001) using the Cockcroft-Gault equation and 9 and 7.2 ml/min in the early and late-start groups, respectively (mean difference, 1.8 ml/min; 95%CI, 1.4 to 2.2; p <0.001) utilizing the MDRD equation. In the early and late-start groups, 195 and 171 patients initiated renal replacement therapy with peritoneal dialysis. Of all the patients, 307 died during the follow-up period, 152 in the early-start group and 155 in the late-start group (cardiovascular death was the most common event). There was no significant difference in survival between the two groups (HR in the early-start group 1.04: 95% CI, 0.83 to 1.30; p = 0.75). The time of dialysis did not influence secondary events (cardiovascular, infectious) or quality of life. The conclusion from the study was that early initiation of dialysis had no significant effect on the rate of death from any cause. The results of the IDEAL study do not imply that initiation of dialysis can be delayed until an estimated GFR of 5 to 7 ml/min/1.73 m^2. 765 of patients in the late-start group had to initiate dialysis when the GFR was above 5 to 7 ml/min/1.73 m^2. due to the development of uremia and fluid overload among other causes. This represents a necessary protocol violation. Also the mean difference of eGFR between both groups was only 2.2 ml/min/1.73 m^2, with six months apart before the start of dialysis. The reality is that waiting to initiate dialysis until signs of uremia appear does not jeopardize the patient. "Early referral to a nephrologist, a well organized patient-education program, and careful planning before dialysis is initiated, are the cornestones of such strategy" as stated by Lameire, et al.[19]. The results of the study are difficult to compare with previous registry studies since it considers both eGFR and symptoms. There were no reports of baseline GFR prior to the initiation of dialysis, quality of life scores, differences in survival outcomes between young, elderly patients, and types of dialysis techniques (hemodialysis vs peritoneal dialysis). This data echoes a previous study by Korevar, et al. that showed similar results, differing in health-related quality of life parameters in the first 12 months of the initiation of dialysis[20]. In conclusion, early initiation of dialysis is not associated with improved survival.

LIMITATIONS OF THE CURENT LITERATURE

The level of evidence of the retrospective studies mentioned is II-2 (based on The US Preventive Services Task force). The IDEAL study probably represents a level I[21].

Lead-time bias, the interval between the start of a study and a defined event, is a limitation in these studies. An error in the conclusions may occur if patients are entered at different stages in the course of the illness. A prolonged survival may be due to early registration of the patient. In dialysis, measuring survival from the start of the treatment increases apparent survival of those started with more residual renal function[11]. Other limitations include age (older men started at higher GFR) of the study population[22], sex (with lower survival rates in female patients) and comorbidities like diabetes mellitus, all of which may influence survival. The type of dialysis modality may also influence outcomes, with peritoneal dialysis showing better outcomes initially[23]. Incomplete information should also be considered because of primary data errors at the time of dialysis. Another important factor is the non-standardized methods of measuring serum creatinine, and the subsequent calculated results of eGFR. The MDRD formula has not been validated in patients with advanced renal failure. For example, the four-variable MDRD equation was developed from non-Asian subjects, and it may hamper results in some studies[24]. Additionally, previous data from USRDS showed that very ill patients were started on dialysis at higher GFR as estimated by MDRD formulas. The result was a spurious association of malnutrition with higher MDRD GFR due to low creatinine production, which can lead to an erroneous interpretation of the effect of timing of dialysis on mortality[12]. Different confounding variables, similar to those listed above, should be considered in order to clearly interpret the present data.

CONCLUSIONS

The optimal time for initiation of chronic dialysis remains unknown. There is a trend in the nephrology literature toward earlier initiation of dialysis[25]. However, prospective data that could guide physicians are not available. Dialysis has many side effects, and it was not possible to predict that starting dialysis earlier failed to improve survival. Previous studies have been confounded by lead-time bias. If early initiation of dialysis did improve survival, then the effect would need to be sufficiently large to justify its use for patients, and for healthcare funding. The practice of earlier initiation of dialysis for ESRD has enormous personal, social and economic implications, with no survival advantage. The latest IDEAL study corroborated the need to reconsider early initiation, except in situations of failed attempts to control volume and electrolyte abnormalities related to uremic conditions.

KEY CONCEPTS

1. There has been an increased incidence of early initiation of dialysis in the last ten years in the ESKD U.S. population.
2. The early initiation of renal replacement therapy (glomerular filtration rate below 10 ml/min/1.73 m^2), was based on retrospective studies that did included residual renal function as a confounding factor.
3. Early initiation of dialysis with elevated GFR's does not improve survival except in the presence of comorbidities and signs of uremia.

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